CASE 4-16180/-/CIP

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EL 813004944US
Express Mail Label Number

October 17, 2001
Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE U.S. PATENT NO. 4,939,130

ISSUED: JULY 3, 1990

INVENTORS: KNUT A. JAEGGI AND LEO WIDLER

FOR: SUBSTITUTED ALKANEDIPHOSPHONIC ACIDS AND PHARMACEUTICAL USE

Box Patent Ext.
Assistant Commissioner for Patents
Washington, D.C. 20231

TRANSMITTAL LETTER FOR PATENT TERM EXTENSION APPLICATION

Sir:

Enclosed in triplicate is an application for the extension of U.S. Patent No. 4,939,130 under 35 U.S.C. §156.

The Commissioner is hereby authorized to charge the Application Fee of $1,120.00 prescribed by 37 C.F.R. §1.20(j)(1), as well as any additional fees which may be necessitated in connection with the filing of this Application for Patent Term Extension, to Applicant's Deposit Account No. 19-0134 in the name of Novartis Corporation. Two additional copies of this transmittal letter are being submitted for charging purposes.

Respectfully submitted,

Carol A. Loeschorn

Carol A. Loeschorn
Attorney for Applicant
Reg. No. 35,590

Novartis Corporation
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027
(908) 522-6932

Date: October 17, 2001

Encl.: Patent Term Extension Application including Appendices A-F in triplicate
Two additional copies of this transmittal letter
Postcard

CASE 4-16180/-/CIP

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

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October 17, 2001
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

RE U.S. PATENT NO. 4,939,130

ISSUED: JULY 3, 1990

INVENTORS: KNUT A. JAEGGI AND LEO WIDLER

FOR: SUBSTITUTED ALKANEDIPHOSPHONIC ACIDS AND PHARMACEUTICAL USE

Box Patent Ext.
Assistant Commissioner for Patents
Washington, D.C. 20231

TRANSMITTAL LETTER FOR PATENT TERM EXTENSION APPLICATION

Sir:

Enclosed in triplicate is an application for the extension of U.S. Patent No. 4,939,130 under 35 U.S.C. §156.

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Respectfully submitted,

Carol A. Loeschorn

Carol A. Loeschorn
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Novartis Corporation
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027
(908) 522-6932

Date: October 17, 2001

Encl.: Patent Term Extension Application including Appendices A-F in triplicate
Two additional copies of this transmittal letter
Postcard

CASE 4-16180/-/CIP

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

EL 813100494 US
Express Mail Label Number

October 17, 2001
Date of Deposit

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE U.S. PATENT NO. 4,939,130

ISSUED: JULY 3, 1990

INVENTORS: KNUT A. JAEGGI AND LEO WIDLER

FOR: SUBSTITUTED ALKANEDIPHOSPHONIC ACIDS AND PHARMACEUTICAL USE

Box Patent Ext.
Assistant Commissioner for Patents
Washington, D.C. 20231

PATENT TERM EXTENSION APPLICATION UNDER 35 U.S.C.§156

Sir:

Pursuant to 35 U.S.C.§156 and 37 C.F.R.§1.710 *et seq.*, Novartis Corporation ("Applicant"), a Corporation of the State of New York, hereby requests an extension of the patent term due to regulatory review of U.S. Patent No. 4,939,130, which was granted on July 3, 1990.

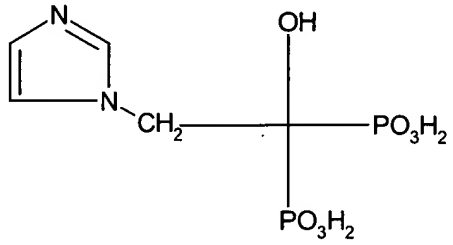
Applicant asserts that it is the owner of the entire right, title and interest in U.S. Patent No. 4,939,130 by virtue of an assignment from the inventors, Knut A. Jaeggi and Leo Widler, to Ciba-Geigy Corporation, which later changed its name to Novartis Corporation. The assignment from the inventors is recorded in the U.S. Patent and Trademark Office at Reel 5228, Frame 0929 and the change of name from Ciba-Geigy Corporation to Novartis Corporation was recorded in the U.S. Patent and Trademark Office at Reel 011089, Frame 0648. Copies of each of these documents evidencing that title to U.S. Patent No. 4,939,130 is vested in Novartis Corporation are attached hereto as Appendix A.

An originally executed Power of Attorney evidencing that the undersigned is an attorney authorized to act on behalf of Novartis Corporation is attached hereto as Appendix B.

In accordance with 35 U.S.C.§156 and 37 C.F.R.§1.740, Applicant provides the following information in support of its request for a patent term extension. The following sections are numbered analogously to 37 C.F.R.§1.740.

(1) Identification of the Approved Product

The approved product is Zometa®, which contains the active ingredient zoledronic acid, having the chemical name 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid and having the chemical structure



2. Identification of the Federal Statute under which Regulatory Review Occurred

The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, Section 505(b) (21 U.S.C.§355(b)).

3. The Date of Permission for Commercial Marketing

The approved product received permission for commercial marketing under Section 505(c) of the Federal Food, Drug and Cosmetic Act (21 U.S.C.§355(c)) on August 20, 2001. A copy of the FDA approval letter is attached hereto as Appendix C.

4. Active Ingredient Statement

The sole active ingredient in Zometa® is zoledronic acid, which has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum Toxin Act prior to the approval of NDA 21-223 by the United States Food and Drug Administration on August 20, 2001.

5. Statement of Timely Filing

The last day on which this application could be submitted is October 19, 2001, which is 60 days after the approval of NDA 21-223 on August 20, 2001. This application is timely filed on or prior to October 19, 2001.

6. Identification of Patent for which Extension is Sought

The patent, the term of which the instant application seeks to extend, is U.S. Patent No. 4,939,130, issued July 3, 1990, having as inventors, Knut A. Jaeggi and Leo Widler and entitled SUBSTITUTED ALKANEDIPHOSPHONIC ACIDS AND PHARMACEUTICAL USE, the term of which would otherwise expire on November 13, 2007.

7. Patent Copy

A complete copy of U.S. Patent No. 4,939,130, identified in paragraph 6 above, is attached as Appendix D.

8. Post-Issuance Activity Statement

No Certificate of Correction; Terminal Disclaimer, Reexamination Certificate or Reissue has been issued or requested with respect to U.S. Patent No. 4,939,130. The first maintenance fee for U.S. Patent No. 4,939,130 in the amount of $930.00 was paid on December 28, 1993 and debited to Applicant's Deposit Account in January 1994. The second maintenance fee in the amount of $2100.00 was paid on December 30, 1997 and debited to Applicant's Deposit Account on January 16, 1998. Copies of the Maintenance fee statements indicating the maintenance fees were paid are attached as Appendix E.

9. Statement Showing How the Claims of the Patent for which Extension is Sought Cover the Approved Product

Claims 1, 2, 4 and 5 claim the approved product. More specifically, claims 1 and 2 claim compounds or a compound which includes the active ingredient, zoledronic acid, in the approved product. The approved product, zoledronic acid, is the compound of claim 1 wherein R_1 is 1-imidazolyl, and R_2 is hydroxy and is the compound of claim 2. Claim 4 claims a pharmaceutical composition containing a compound of claim 1. Claim 5 claims a method of treating diseases associated with impaired calcium metabolism comprising administering a compound of claim 1.

10. Statement of the Relevant Dates to Determine the Regulatory Review Period

The relevant dates and information pursuant to 35 U.S.C.§156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(i) The patent for which extension of the term thereof is sought claims a human drug product, a pharmaceutical composition containing such human drug product and a method of treating diseases associated with impaired calcium metabolism using such human drug product. The human drug product is zoledronic acid.

(A) An Investigational New Drug Application for zoledronic acid was submitted on August 12, 1993, received by the Department of Health and Human Services on August 19, 1993 and was assigned IND No. 43,240 and became effective on September 18, 1993. The original IND was filed for Paget's Disease. The first submission for Hypercalcemia of Malignancy, the approved indication, was made on December 18, 1997.

(B) A New Drug Application for zoledronic acid was submitted to the Department of Health and Human Services on December 21, 1999 and granted NDA No. 21-223.

(C) NDA No. 21-223 was approved on August 20, 2001.

11. Brief Description of Activities Undertaken During the Regulatory Review Period

As a brief description of the activities undertaken during the applicable regulatory review period, attached hereto as Appendix F is a chronology of the major communications between the U.S. Food and Drug Administration and the Applicant in IND No. 43,240 and NDA No. 21-223.

12. Opinion of Eligibility for Extension

Applicant is of the opinion that U.S. Patent No. 4,939,130 is eligible for extension under 35 U.S.C.§156 and 37 C.F.R.§1.720 because it satisfies all of the requirements for such extension as follows:

(a) 35 U.S.C.§156(a) and 37 C.F.R.§1.720(a)

U.S. Patent No. 4,939,130 claims a human drug product, zoledronic acid, pharmaceutical compositions thereof and methods of use thereof.

(b) 35 U.S.C.§156(a)(1) and 37 C.F.R.§1.720(g)

The term of U.S. Patent No. 4,939,130 (expiring November 13, 2007) has not expired before the submission of this application.

(c) 35 U.S.C.§156(a)(2) and 37 C.F.R.§1.720(b)

The term of U.S. Patent No. 4,939,130 has never been extended.

(d) 35 U.S.C.§156(a)(3) and 37 C.F.R.§1.720(c)

The application for extension of the term of U.S. Patent No. 4,939,130 is submitted by the authorized attorney of the owner of record thereof in accordance with the requirements of 35 U.S.C.§156(d) and 37 C.F.R.§1.740.

(e) 35 U.S.C.§156(a)(4) and 37 C.F.R.§1.720(d)

The approved product, Zometa®, has been subjected to a regulatory review period before its commercial marketing or use.

(f) 37 C.F.R.§1.720(h)

No other patent has been extended for the same regulatory review period for the approved product, Zometa®.

(g) 35 U.S.C.§156(a)(5)(A) and 37 C.F.R.§1.720(e)(1)

The permission for the commercial marketing or use of the approved product, Zometa®, is the first received permission for commercial marketing or use of Zometa®.

(h) Length of extension claimed under 37 C.F.R.§1.740(a)(12)

The length of extension of the patent term of U.S. Patent No. 4,939,130 requested by Applicant is 1,752 days, which length was calculated in accordance with 37 C.F.R.§1.775 as follows:

(a) The regulatory review period under 35 U.S.C.§156(g)(1)(B) began on September 18, 1993 (the effective date of the IND) and ended on August 20, 2001, amounting to a total of 2,895 days which is the sum of (i) and (ii) below:

(i) The period of review under 35 U.S.C.§156(g)(1)(B)(i), the "Testing Period," began on September 18, 1993 and ended on December 21, 1999 which is 2,286 days;

(ii) The period for review under 35 U.S.C.§156(g)(1)(B)(ii), the "Application Period," began on December 21, 1999 and ended on August 20, 2001, which is 609 days;

(b) The regulatory review period upon which the period for extension is calculated is the entire regulatory review period as determined in subparagraph (13)(a) above (2,895 days) less:

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (July 3, 1990), i.e., zero days, and

(ii) The number of days during which the Applicant did not act with due diligence, i.e., zero days, and

(iii) One-half of the number of days remaining in the period in subparagraph (13)(a)(i) after subtracting the number of days in subparagraphs (13)(b)(i) and (13)(b)(ii), which is one-half of (2,286 - [0 + 0]) or 1,143 days;

which results in a period of 2,895 -[0 + 0 + 1,143] = 1,752 days.

(c) The number of days as determined in subparagraph (13)(b), when added to the original term (November 13, 2007), would result in the date of August 30, 2012.

(d) Fourteen (14) years when added to the date of the NDA Approval Letter (August 20, 2001) would result in the date of August 20, 2015.

(e) The earlier date as determined by subparagraphs (13)(c) and (13)(d) is August 30, 2012.

(f) Since the original patent was issued after September 24, 1984, the extension otherwise obtainable is limited to not more than five (5) years. Five years, when added to the original expiration of U.S. Patent No. 4,939,130 (November 13, 2007), results in the date November 13, 2012.

(g) The earlier date as determined in subparagraphs (13)(e) and (13)(f) is August 30, 2012.

13. Duty of Disclosure Acknowledgement Under 37 C.F.R.§1.740(a)(13)

Applicant acknowledges a duty to disclose to the Commissioner of Patent and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

14. Fee Charge

The prescribed fee for receiving and acting upon this application is to be charged to Applicant's Deposit Account No. 19-0134 as authorized in the attached transmittal letter, submitted in triplicate.

15. Correspondence Address Required by 37 C.F.R.§1.740(a)(15)

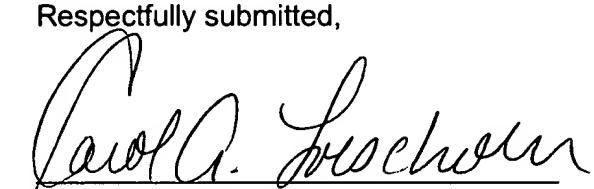
All correspondence relating to this application for patent term extension should be addressed to:

Thomas Hoxie
Novartis Pharmaceuticals Corp.
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027

16. Certification Under 37 C.F.R.§1.740(b)

The undersigned hereby certifies that the instant application, including its attachments and supporting papers, is being submitted as one original and two copies thereof in accordance with 37 C.F.R.§1.740(b).

Respectfully submitted,



Novartis Pharmaceuticals Corporation
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027
(908) 522-6932

Carol A. Loeschorn
Attorney for Applicant
Reg. No. 35,590

Date: October 17, 2001

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Offic
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPENDIX A

TO: KARL F. JORDA
444, SAW MILL RIVER RD.
ARDSLEY, NY 10502

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW. A DIGEST OF THE DOCUMENT HAS ALSO BEEN MADE AND APPEARS IN THE OFFICE'S RECORDS AS SHOWN:

ASSIGNOR: 001 JAEGGI, KNUT A. DOC DATE: 02/22/89
ASSIGNOR: 002 WIDLER, LEO DOC DATE: 02/22/89

RECORDATION DATE: 02/14/90 NUMBER OF PAGES 001 REEL/FRAME 5228/0929

DIGEST: ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE: 501 CIBA-GEIGY CORPORATION, 444 SAW MILL RIVER ROAD, ARDSLEY, NEW YORK 10502 A CORP. OF NY

SERIAL NUMBER 7-315962 FILING DATE 02/27/89
PATENT NUMBER ISSUE DATE 00/00/00

TITLE OF INVENTION: SUBSTITUTED ALKANEDIPHOSPHONIC ACIDS AND PHARMACEUTICAL USE

INVENTOR: 001 JAEGGI, KNUT A.
INVENTOR: 002 WIDLER, LEO

4-16180/-1/cip

Copy Sent to Basle
5-3-90 D.C.

CIBA-GEIGY Corporation
Ardsley, New York 10502-2699
Telephone 914 347 4700

CIBA-GEIGY

APPENDIX A

Commissioner of Patents and Trademarks

Washington, D.C. 20231

[redacted]

RE: U.S. Patent Application

Serial No.: 315,962

Filed: February 27, 1989

Case No.: 4-16180/-/CIP

ASSIGNMENT TRANSMITTAL

Sir:

I CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO COMMISSIONER OF PATENTS AND TRADEMARKS, WASHINGTON, D.C. 20231. ON February 8, 1990.

Enclosed, for recordation is the Assignment in this case. The patent should be issued to:

CIBA-GEIGY Corporation
444 Saw Mill River Road
Ardsley, New York 10502

The $8.00 Recordation Fee should be charged to Deposit Account No.: 07-0590.

A triplicate copy of this letter is enclosed herewith for charging purposes.

91492308

Very truly yours,

CIBA-GEIGY Corporation

G 11261 02/27/90 07315962 07-0590 110 518 8.00CH

JoAnn Villamizar
Reg.No. 30,598
Patent Department

APPENDIX A

US Case 4-16180/-/CIP

ASSIGNMENT

I (We) Knut A. Jaeggi of 4054 Basle, Switzerland and
Leo Widler of 4142 Münchenstein, Switzerland

for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to CIBA-GEIGY Corporation, a New York corporation, of 444 Saw Mill River Road, Ardsley, New York, 10502, U.S.A.,its successors, assigns and legal representatives, all my (our) right, title and interest, in and for the United States of America, in and to the

Novel substituted alkanediphosphonic acids

invented by me (us) and described in the application for United States Letters Patent therefor, executed on even date herewith, and all United States Letters Patent which may be granted therefor, and all divisions, reissues, continuations and extensions thereof, the said interest being the entire ownership of the said Letters Patent when granted, to be held and enjoyed by the said CIBA-GEIGY Corporation, its successors, assigns or other legal representatives, to the full end of the term for which said Letters Patent may be granted, as fully and entirely as the same would have been held and enjoyed by me (us) if this assignment and sale had not been made;

And I (we) hereby authorize and request the Commissioner of Patents and Trademarks to issue said Letters Patent to the said CIBA-GEIGY Corporation.

Signed on 22.2.89

Knut A. Jaeggi

Leo Widler

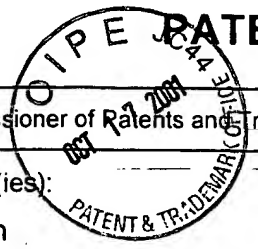
FORM PTO-1595
(Rev. 6-93)

OMB No. 0651-0011 (exp. 4/94)

RECORDATION FORM COVER SHEET
PATENTS ONLY

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

APPENDIX A



To the Honorable Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
Ciba-Geigy Corporation

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

3. Nature of conveyance:

☐ Assignment ☐ Merger

☐ Security Agreement ☒ Change of Name

☐ Other _____

Execution Date: _____

2. Name and address of receiving party(ies)

Name: Novartis Corporation

Internal Address: _____

Street Address: 608 Fifth Avenue

City: New York State: NY ZIP: 10020

Additional name(s) & address(es) attached? ☐ Yes ☒ No

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: _____

A. Patent Application No.(s)

B. Patent No.(s)
D352,107 4,409,212 4,424,221 4,444,775

Additional numbers attached? ☒ Yes ☐ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Thomas Hoxie

Internal Address: Novartis Corporation

Patent and Trademark Dept.

Street Address: 564 Morris Avenue

City: Summit State: NJ ZIP: 07901-1027

6. Total number of applications and patents involved: 337

7. Total fee (37 CFR 3.41) $ 13,480

☐ Enclosed

☒ Authorized to be charged to deposit account and any other additional fees required.

8. Deposit account number:
19-0134 (in the name of Novartis Corporation)
(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Melvyn M. Kassenoff
Name of Person Signing
Reg. No. 26,389

Melvyn M. Kassenoff
Signature

August 18, 2000
Date

☐ **Certificate of mailing on reverse side**

Total number of pages including cover sheet, attachments, and document: 5

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents & Trademarks, Box Assignments
Washington, D.C. 20231

APPENDIX A

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

101484946A

NOVEMBER 14, 2000

NOVARTIS CORPORATION
THOMAS HOXIE
564 MORRIS AVENUE
SUMMIT, NJ 07901-1027

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 08/22/2000

REEL/FRAME: 011089/0648
NUMBER OF PAGES: 5

BRIEF: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
CIBA-GEIGY CORPORATION

DOC DATE: 06/12/1997

ASSIGNEE:
NOVARTIS CORPORATION
608 FIFTH AVENUE
NEW YORK, NEW YORK 10020

SERIAL NUMBER: 29002441
PATENT NUMBER: D352107

FILING DATE: 12/10/1992
ISSUE DATE: 11/01/1994

SERIAL NUMBER: 06366792
PATENT NUMBER: 4409212

FILING DATE: 04/09/1982
ISSUE DATE: 10/11/1983

SERIAL NUMBER: 06426424
PATENT NUMBER: 4424221

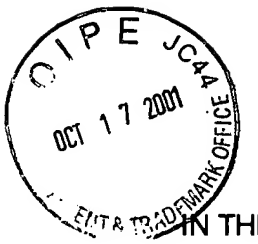
FILING DATE: 09/28/1982
ISSUE DATE: 01/03/1984

SERIAL NUMBER: 06382972
PATENT NUMBER: 4444775

FILING DATE: 06/01/1982
ISSUE DATE: 04/24/1984

APPENDIX A

SERIAL NUMBER: 06918584 PATENT NUMBER: 4697020	FILING DATE: 10/09/1986 ISSUE DATE: 09/29/1987
SERIAL NUMBER: 06842337 PATENT NUMBER: 4729892	FILING DATE: 03/21/1986 ISSUE DATE: 03/08/1988
SERIAL NUMBER: 06895979 PATENT NUMBER: 4778809	FILING DATE: 08/13/1986 ISSUE DATE: 10/18/1988
SERIAL NUMBER: 07156770 PATENT NUMBER: 4784808	FILING DATE: 02/18/1988 ISSUE DATE: 11/15/1988
SERIAL NUMBER: 07059898 PATENT NUMBER: 4804661	FILING DATE: 06/09/1987 ISSUE DATE: 02/14/1989
SERIAL NUMBER: 07080240 PATENT NUMBER: 4839379	FILING DATE: 07/28/1987 ISSUE DATE: 06/13/1989
SERIAL NUMBER: 07185205 PATENT NUMBER: 4857660	FILING DATE: 04/22/1988 ISSUE DATE: 08/15/1989
SERIAL NUMBER: 07229189 PATENT NUMBER: 4873086	FILING DATE: 08/08/1988 ISSUE DATE: 10/10/1989
SERIAL NUMBER: 07212028 PATENT NUMBER: 4897486	FILING DATE: 06/23/1988 ISSUE DATE: 01/30/1990
SERIAL NUMBER: 07317387 PATENT NUMBER: 4918097	FILING DATE: 03/01/1989 ISSUE DATE: 04/17/1990
SERIAL NUMBER: 07315962 PATENT NUMBER: 4939130	FILING DATE: 02/27/1989 ISSUE DATE: 07/03/1990
SERIAL NUMBER: 07232266 PATENT NUMBER: 4965074	FILING DATE: 08/15/1988 ISSUE DATE: 10/23/1990
SERIAL NUMBER: 07145432 PATENT NUMBER: 4971981	FILING DATE: 01/19/1988 ISSUE DATE: 11/20/1990
SERIAL NUMBER: 07432297 PATENT NUMBER: 4978677	FILING DATE: 11/06/1989 ISSUE DATE: 12/18/1990
SERIAL NUMBER: 07242833 PATENT NUMBER: 4996058	FILING DATE: 09/12/1988 ISSUE DATE: 02/26/1991
SERIAL NUMBER: 07367163 PATENT NUMBER: 5026841	FILING DATE: 06/16/1989 ISSUE DATE: 06/25/1991
SERIAL NUMBER: 07491145 PATENT NUMBER: 5064761	FILING DATE: 03/09/1990 ISSUE DATE: 11/12/1991
SERIAL NUMBER: 07510501 PATENT NUMBER: 5071861	FILING DATE: 04/18/1990 ISSUE DATE: 12/10/1991



APPENDIX B

CASE 4-16180/-/CIP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE U.S. PATENT NO. 4,939,130

ISSUED: JULY 3, 1990

INVENTORS: KNUT A. JAEGGI AND LEO WIDLER

FOR: SUBSTITUTED ALKANEDIPHOSPHONIC ACIDS AND PHARMACEUTICAL USE

Assistant Commissioner for Patents
Washington, D.C. 20231

POWER OF ATTORNEY

Sir:

Novartis Corporation, a New York Corporation having offices at 608 Fifth Avenue, New York, New York 10020, being the owner of the entire title and interest in and to U.S. Patent No. 4,939,130, which was granted on July 3, 1990 toKnut A. Jaeggi and Leo Widler and entitled "SUBSTITUTED ALKANEDIPHOSPHONIC ACIDS AND PHARMACEUTICAL USE", hereby appoints the attorneys and agents associated with customer No. 001095, respectively and individually, each of them with full power of substitution and revocation, to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected herewith.

Please direct all telephone calls to Carol A. Loeschorn at (908) 522-6932, and all correspondence to Thomas Hoxie at Novartis Pharmaceuticals Corporation, Patent and Trademark Department, 564 Morris Avenue, Summit, NewJersey 07901-1027.

Thomas Hoxie
Vice President, Novartis Corporation
Reg. No. 32,993

APPENDIX C

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-223

Novartis Pharmaceuticals Corporation
Attention: Ms. Eileen Ryan
Associate Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Ryan:

Please refer to your new drug application (NDA) dated and received December 21, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zometa (zoledronic acid for injection).

We acknowledge receipt of your submissions dated September 14, 21, and 29, November 6, and December 13 and 21, 2000, and February 19, March 26 and 29, April 2, 9, 11, 25, and 30, May 3, June 1 and 12, July 10, and August 3, 17, and 20, 2001. Your submission of February 19, 2001, constituted a complete response to our September 21, 2000, action letter.

This new drug application provides for the use of Zometa (zoledronic acid for injection) for the treatment of hypercalcemia of malignancy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed-upon draft labeling text submitted August 20, 2001, vial labels submitted August 3, 2001, and carton labels submitted August 20, 2001, for the treatment of hypercalcemia of malignancy when administered as a 4 mg dose over no less than 15 minutes. Accordingly, the application is approved effective on the date of this letter. The final printed labeling (FPL) must be identical to the submitted draft labeling. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-223." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitment in your submission dated August 17, 2001, in which you agree to conduct a pharmacokinetics and pharmacodynamic study of Zometa in patients with impaired renal function. The study may be either single- or multiple-dose. The final study report

should be submitted within one month of the date of this letter.

Submit clinical protocols to your IND for this product. Submit study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of the commitment in your annual report to this NDA. The status summary should include expected study completion and final report submission dates, any changes in plans since the last annual report, and, the number of patients entered into each study. All submissions, including supplements, relating to this postmarketing study commitment must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). On November 30, 1999, you requested a waiver from conducting pediatric studies for the indication, treatment of hypercalcemia of malignancy. The waiver was granted for patients ages 0 – 16 years on February 25, 2000.

Please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

In addition we have concluded that the proposal to recommend an 8-mg intravenous dose for patients requiring retreatment of hypercalcemia of malignancy is approvable. The similar response rates following single infusions of 4-mg and 8-mg, the lack of a comparison arm in the retreatment portion of the two controlled, multicenter studies, and the increased risk of renal toxicity with the 8-mg dose compared to the 4-mg dose, do not support the safety and efficacy of the 8-mg dose for retreatment. A study demonstrating that the 8-mg dose is superior to the 4-mg dose in patients requiring retreatment and data to support the safety of the 8-mg dose would be necessary to support approval of the 8-mg dose for patients who require retreatment for hypercalcemia of malignancy.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your

intent to file an amendment, or follow one of your other options under 21 CFR 314.110. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiences have been addressed.

If you have any questions, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

John K. Jenkins, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Jenkins
8/20/01 04:59:09 PM

APPENDIX D

United States Patent [19]

Jaeggi et al.

[11] **Patent Number: 4,939,130**

[45] **Date of Patent: Jul. 3, 1990**

[54] **SUBSTITUTED ALKANEDIPHOSPHONIC ACIDS AND PHARMACEUTICAL USE**

[75] Inventors: **Knut A. Jaeggi, Basel; Leo Widler, Müchenstein, both of Switzerland**

[73] Assignee: **Ciba-Geigy Corporation, Ardsley, N.Y.**

[21] Appl. No.: **315,962**

[22] Filed: **Feb. 27, 1989**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 120,284, Nov. 13, 1987, abandoned.

[30] **Foreign Application Priority Data**

Nov. 21, 1986 [CH] Switzerland 4666/86

[51] Int. Cl.[5] A61K 31/675; C07F 9/65

[52] U.S. Cl. 514/94; 514/92; 514/93; 548/112; 548/119

[58] Field of Search 548/119, 112; 514/92, 514/93, 94

[56] **References Cited**

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186405	7/1986	European Pat. Off. .
0258618	3/1988	European Pat. Off. .
3203307	7/1983	Fed. Rep. of Germany .
3428524	2/1986	Fed. Rep. of Germany .

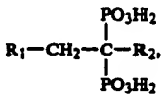
OTHER PUBLICATIONS

CA 105:134140r (1986).

Primary Examiner—Richard L. Raymond
Attorney, Agent, or Firm—JoAnn Villamizar

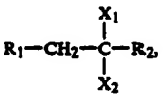
[57] **ABSTRACT**

Alkanediphosphonic acids, in particular heteroarylalkanediphosphonic acids of formula



(I)

wherein R_1 is a 5-membered heteroaryl radical which may be fused with benzene or cyclohexene nuclei and which contains, as hetero atoms, 2 to 4 N-atoms or 1 or 2 N-atoms as well as 1 O- or S-atom, and which is unsubstituted or C-substituted by lower alkyl, phenyl or phenyl which is substituted by lower alkyl, lower alkoxy and/or halogen, or by lower alkoxy, hydroxy, di-lower alkylamino, lower alkylthio and/or halogen, and/or is N-substituted at a N-atom which is capable of substitution by lower alkyl, lower alkoxy and/or halogen, and R_2 is hydrogen, hydroxy, amino, lower alkylthio or halogen, and salts thereof, have regulatory action on calcium metabolism and can be used as medicaments for the treatment of diseases associated with impairment of calcium metabolism. The compounds are obtained for example by converting, in a compound of formula



(II)

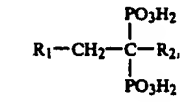
wherein X_1 is a functionally modified phosphono group and X_2 is a free or functionally modified phosphono group, X_1 and, if appropriate X_2, into the free phosphono group.

5 Claims, No Drawings

SUBSTITUTED ALKANEDIPHOSPHONIC ACIDS AND PHARMACEUTICAL USE

This is a Continuation-in-Part-Application of our patent application Ser. No. 07/120,284, filed November 13, 1987, now abandoned.

The present invention relates to novel substituted alkanediphosphonic acids, in particular to heteroarylalkanediphosphonic acids of formula



(I)

wherein R_1 is a 5-membered heteroaryl radical which contains, as hetero atoms, 2 to 4 N-atoms or 1 or 2 N-atoms as well as 1 O- or S-atom, and which is unsubstituted or C-substituted by lower alkyl, phenyl or phenyl which is substituted by lower alkyl, lower alkoxy and/or halogen, or by lower alkoxy, hydroxy, di-lower alkylamino, lower alkylthio and/or halogen, and/or is N-substituted at a N-atom which is capable of substitution by lower alkyl, lower alkoxy and/or halogen, and R_2 is hydrogen, hydroxy, amino, lower alkylthio or halogen, and to the salts thereof, to the preparation of said compounds, to pharmaceutical compositions containing them, and to the use thereof as medicaments.

Examples of 5-membered heteroaryl radicals containing 2 to 4 N-atoms or 1 or 2 N-atoms as well as 1 O- or S-atom as hetero atoms are: imidazolyl, e.g. imidazol-1-yl, imidazol-2-yl or imidazol-4-yl, pyrazolyl, e.g. pyrazol-1-yl or pyrazol-3-yl, thiazolyl, e.g. thiazol-2-yl or thiazol-4-yl, or, less preferably, oxazolyl, e.g. oxazol-2-yl or oxazol-4-yl, isoxazolyl, e.g. isooxazol-3-yl or isooxazol-4-yl, triazolyl, e.g. 1H-1,2,4-triazol-1-yl, 4H-1,2,4-triazol-3-yl or 4H-1,2,4-triazol-4-yl or 2H-1,2,3-triazol-4-yl, tetrazolyl, e.g. tetrazol-5-yl, thiadiazolyl, e.g. 1,2,5-thiadazol-3-yl, and oxdiazolyl, e.g. 1,3,4-oxadiazol-2-yl. These radicals may contain one or more identical or different, preferably one or two identical or different, substituents selected from the group mentioned at the outset. Radicals R_1, unsubstituted or substituted as indicated, are e.g. imidazol-2-yl or imidazol-4-yl radicals which are unsubstituted or C-substituted by phenyl or phenyl which is substituted as indicated, or which are C- or N-substituted by C_1–C_4alkyl, e.g. methyl, and are typically imidazol-2-yl, 1-C_1–C_4alkylimidazol-2-yl such as 1-methylimidazol-2-yl, or 2- or 5-C_1–C_4alkylimidazol-4-yl such as 2- or 5-methylimidazol-4-yl, unsubstituted thiazolyl radicals, e.g. thiazol-2-yl, or 1H-1,2,4-triazol radicals, unsubstituted or substituted by C_1–C_4alkyl such as methyl, e.g. 1-C_1–C_4alkyl-1H-1,2,4-triazol-5-yl such as 1-methyl-1H-1,2,4-triazol-5-yl, or imidazol-1-yl, pyrazolyl-1-yl, 1H-1,2,4-triazol-1-yl, 4H-1,2,4-triazol-4-yl or tetrazol-1-yl radicals, unsubstituted or C-substituted by phenyl or phenyl which is substituted as indicated or by C_1–C_4alkyl such as methyl, for example imidazol-1-yl, 2-, 4- or 5-C_1–C_4alkylimidazol-1-yl such as 2-, 4- or 5-methylimidazol-1-yl, pyrazol-1-yl, 3- or 4-C_1–C_4alkylpyrazol-1-yl such as 3- or 4-methylpyrazol-1-yl, 1H-1,2,4-tetrazol-1-yl, 3-C_1–C_4alkyl-1H-1,2,4-triazol-1-yl such as 3-methyl-1H-1,2,4-triazol-1-yl, 4H-1,2,4-triazol-1-yl, 3-C_1–C_4alkyl-4H-1,2,4-triazol-4-yl such as 3-methyl-4H-1,2,4-triazol-4-yl or 1H-1,2,4-tetrazol-1-yl.

Radicals and compounds hereinafter qualified by the term "lower" will be understood as meaning typically those containing up to 7 carbon atoms inclusive, preferably up to 4 carbon atoms inclusive. The general terms have for example the following meanings:

Lower alkyl is for example C_1–C_4alkyl such as methyl, ethyl, propyl or butyl, and also isobutyl, sec-butyl or tert-butyl, and may further be C_5–C_7alkyl such as pentyl, hexyl or heptyl.

Phenyl-lower alkyl is for example phenyl-C_1–C_4alkyl, preferably 1-phenyl-C_1–C_4alkyl such as benzyl.

Lower alkoxy is for example C_1–C_4alkoxy such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy or tert-butoxy.

Di-lower alkylamino is for example di-C_1–C_4alkylamino such as dimethylamino, diethylamino, N-ethyl-N-methylamino, dipropylamino, N-methyl-N-propylamino or dibutylamino.

Lower alkylthio is for example C_1–C_4alkylthio such as methylthio, ethylthio, propylthio or butylthio, and also isobutylthio, sec-butylthio or tert-butylthio.

Halogen is for example halogen having an atomic number of up to 35 inclusive, such as fluorine, chlorine or bromine.

Salts of compounds of formula I are in particular the salts thereof with pharmaceutically acceptable bases, such as non-toxic metal salts derived from metals of groups Ia, Ib, IIa and IIb, e.g. alkali metal salts, preferably sodium or potassium salts, alkaline earth metal salts, preferably calcium or magnesium salts, copper, aluminium or zinc salts, and also ammonium salts with ammonia or organic amines or quaternary ammonium bases such as free or C-hydroxylated aliphatic amines, preferably mono-, di- or tri-lower alkylamines, e.g. methylamine, ethylamine, dimethylamine or diethylamine, mono-, di- or tri(hydroxy-lower alkyl)amines such as ethanolamine, diethanolamine or triethanolamine, tris(-hydroxymethyl)aminomethane or 2-hydroxy-tert-butylamine, or N-(hydroxy-lower alkyl)-N,N-di-lower alkylamines or N-(polyhydroxy-lower alkyl)-N-lower alkylamines such as 2-(dimethylamino)ethanol or D-glucamine, or quaternary aliphatic ammonium hydroxides, e.g. with tetrabutylammonium hydroxide.

In this connection it should also be mentioned that the compounds of formula I may also be obtained in the form of inner salts, provided the group R_1 is sufficiently basic. These compounds can therefore also be converted into the corresponding acid addition salts by treatment with a strong protic acid such as a hydrohalic acid, sulfuric acid, sulfonic acid, e.g. methanesulfonic acid or p-toluenesulfonic acid, or sulfamic acid, e.g. N-cyclohexylsulfamic acid.

The compounds of formula I and salts thereof have valuable pharmacological properties. In particular, they have a pronounced regulatory action on the calcium metabolism of warm-blooded animals. Most particularly, they effect a marked inhibition of bone resorption in rats, as can be demonstrated in the experimental procedure described in Acta Endrocinol. 78, 613–24 (1975), by means of the PTH-induced increase in the serum calcium level after subcutaneous administration of doses in the range from about 0.01 to 1.0 mg/kg, as well as in the TPTX (thyroparathyroidectomised) rat model by means of hypercalcaemia induced by vitamin D_3 after subcutaneous administration of a dose of about 0.0003 to 1.0 mg. Tumor callcaemia induced by Walker 256 tu-

mors is likewise inhibited after peroral administration of about 1.0 to 100 mg/kg. In addition, when administered subcutaneously in a dosage of about 0.001 to 1.0 mg/kg in the experimental procedure according to Newbould, Brit. J. Pharmacology 21, 127 (1963), and according to Kaibara et al., J. Exp. Med. 159, 1388-96 (1984), the compounds of formula I and salts thereof effect a marked inhibition of the progression of arthritic conditions in rats with adjuvant arthritis. They are therefore eminently suitable for use as medicaments for the treatment of diseases which are associated with impairment of calcium metabolism, for example inflammatory conditions in joints, degenerative processes in articular cartilege, of osteoporosis, periodontitis, hyperparathyroidism, and of calcium deposits in blood vessels or prothetic implants. Favourable results are also achieved in the treatment of diseases in which an abnormal deposit of poorly soluble calcium salts is observed, as in arthritic diseases, e.g. ancylosing spondilitis, neuritis, bursitis, periodontitis and tendinitis, fibrodysplasia, osteoarthrosis or arteriosclerosis, as well as those in which an abnormal decomposition of hard body tissue is the principal symptom, e.g. heriditary hypophosphatasia, degenerative states of articular cartilege, osteoporosis of different provenance, Paget's disease and osteodystrophia fibrosa, and also osteolytic conditions induced by tumors.

The invention relates in particular to compounds of formula I, wherein R_1 is an imidazolyl, pyrazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl or 4H-1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl or thiadiazolyl radical which is unsubstituted or C-substituted by one or two members selected from lower alkyl, lower alkoxy, phenyl or phenyl which is in turn substituted by one or two members selected from lower alkyl, lower alkoxy and/or halogen, hydroxy, di-lower alkylamino, lower alkylthio and/or halogen, and/or is N-substituted at a N-atom which is capable of substitution by lower alkyl or phenyl-lower alkyl which is unsubstituted or substituted by one or two members selected from lower alkyl, lower alkoxy and/or halogen; and R_2 is hydrogen, hydroxy, amino, lower alkylthio or halogen, and salts thereof, especially the inner salts and pharmaceutically acceptable salts thereof with bases.

The invention related more particularly for example to compounds of formula I, wherein R_1 is an imidazolyl, pyrazolyl, 2H-1,2,3-triazolyl or 4H-1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl or thiadiazolyl radical which is unsubstituted or C-substituted by one or two members selected from lower alkyl, lower alkoxy, phenyl or phenyl which is in turn substituted by one or two members selected from lower alkyl, lower alkoxy and/or halogen, hydroxy, di-lower alkylamino, lower alkylthio and/or halogen, and/or is N-substituted at a N-atom which is capable of substitution by lower alkyl or phenyl-lower alkyl which is unsubstituted or substituted by one or two members selected from lower alkyl, lower alkoxy and/or halogen; and R_2 is hydrogen, hydroxy, amino, lower alkylthio or halogen, and salts thereof, especially the inner salts and pharmaceutically acceptable salts thereof with bases.

The invention relates most particularly to compounds of formula I, wherein R_1 is an imidazolyl radical, such as imidazol-1-yl, imidazol-2-yl or imidazol-4-yl, a 4H-1,2,4-triazolyl radical such as 4H-1,2,4-triazol-4-yl, or a thiazolyl radical such as thiazol-2-yl, which radical is unsubstituted or C-substituted by one or two members selected from C_1–C_4alkyl such as methyl, C_1–C_4alkoxy such as methoxy, phenyl, hydroxy, di-C_1–C_4alkylamino such as dimethylamino or diethylamino, C_1–C_4alkylthio such as methylthio, and/or halogen having an atomic number up to 35 inclusive such as chlorine, and/or is N-substituted at a N-atom which is capable of substitution by C_1–C_4alkyl such as methyl, or phenyl-C_1–C_4alkyl such as benzyl; and R_2 is preferably hydroxy or, less preferably, hydrogen or amino, and salts thereof, especially the inner salts and pharmaceutically acceptable salts thereof with bases.

The invention preferably relates on the one hand to compound of formula I, wherein R_1 is an imidazol-2- or -4-yl radical which is unsubstituted or C-substituted by phenyl or C- or N-substituted by C_1–C_4alkyl such as methyl, e.g. imidazol-2-yl, 1-C_1–C_4alkylimidazol-2-yl such as 1-methylimidazol-2-yl, or 2- or 5-C_1–C_4alkylimidazol-4-yl such as 2- or 5-methylimidazol-4-yl, or is an unsubstituted thiazolyl radical, e.g. thiazol-2-yl, or is a 1H-1,2,4-triazolyl radical which is unsubstituted or substituted by C_1–C_4alkyl such as methyl, e.g. 1C_1–C_4alkyl-1H-1,2,4-triazol-5-yl such as 1-methyl-1H-1,2,4-triazol-5-yl, and R_2 is hydroxy or, less preferably, hydrogen, and salts, especially pharmaceutically acceptable salts, thereof.

The invention preferably relates on the other hand to compounds of formula I, wherein R_1 is an imidazol-1-yl, pyrazol-1-yl, 1H-1,2,4-triazol-1-yl, 4H-1,2,4-triazol-4-yl or tetrazol-1-yl radical which is unsubstituted or C-substituted by phenyl or C_1–C_4alkyl such as methyl, e.g. imidazol-1-yl, 2-, 4- or 5-C_1–C_4alkylimidazol-1-yl such as 2-, 4- or 5-methylimidazol-1-yl, pyrazol-1-yl, 3- or 4-C_1–C_4alkylpyrazol-1-yl such as 3- or 4-methylpyrazol-1-yl, 1H-1,2,4-tetrazol-1-yl, 3-C_1–C_4alkyl-1H-1,2,4-triazol-1-yl such as 3-methyl-1H-1,2,4-triazol-1-yl, 4H-1,2,4-triazol-1-yl, 3-C_1–C_4alkyl-4H-1,2,4-triazol-4-yl such as 3-methyl-4H-1,2,4-triazol-4-yl or 1H-tetrazol-1-yl, and R_2 is hydroxy or, less preferably, hydrogen, and salts, especially pharmaceutically acceptable salts, thereof.

The invention relates first and foremost to compounds of formula I, wherein R_1 is an imidazolyl radical which is unsubstituted or substituted by C_1–C_4alkyl such as methyl, e.g. imidazol-1-yl, imidazol-2-yl, 1-methylimidazol-2-yl, imidazol-4-yl or 2- or 5-methylimidazol-4-yl, and R_2 is hydroxy or, less preferably, hydrogen, and salts, especially pharmaceutically acceptable salts, thereof.

The invention relates specifically to the compounds of formula I and the salts thereof, especially the inner salts and pharmaceutically acceptable salts thereof with bases mentioned in the Examples.

The invention further relates to a process based on per se known methods for the preparation of compounds of formula I and salts thereof, which process comprises

(a) in a compound of formula

(II)

wherein X_1 is a functionally modified phosphono group and X_2 is a free or functionally modified phosphono group, which compound may be temporarily protected

at a N-atom of the radical R_1 which is capable of substitution, converting X_1 and, if appropriate X_2, into the free phosphono group; or

(b) reacting a compound of formula

$$R_1—CH_2—X_3 \quad (III),$$

wherein X_3 is a carboxy, carbamyl, imino ether, imino ester or cyano group, which compound may be temporarily protected at a N-atom of the radical R_1 which is capable of substitution, with phosphorous acid and phosphorus trichloride, and where a start is made from a compound of formula III, wherein X_3 is a carbamyl, imino ether, imino ester or cyano group, the subsequent hydrolysis yields a compound of formula I, wherein R_2 is amino, and, if desired, converting a resultant compound into another compound of formula I and/or a resultant free compound into a salt or a resultant salt into the free compound or into another salt.

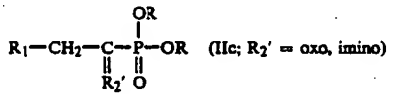
In process variant (a), functionally modified phosphono groups to be converted into phosphono are for example in ester form, preferably in a diester form of formula $—P(=O)(OR)_2$ (IV), wherein OR is e.g. lower alkoxy or a phenoxy group which is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen, trifluoromethyl and/or hydroxy.

The conversion of a functionally modified phosphono group into the free phosphono group is effected in conventional manner by hydrolysis, for example in the presence of a mineral acid such as hydrobromic acid, hydrochloric acid or sulfuric acid, or by reaction with a tri-lower alkylhalosilane, e.g. with trimethylchlorosilane in the presence of sodium iodide, or preferably with trimethyliodosilane or trimethylbromosilane, preferably with cooling, e.g. in the temperature range from about 0° to 25° C.

The starting materials of formula II, wherein R_2 is hydroxy or amino, can be prepared for example by reacting a compound of formula

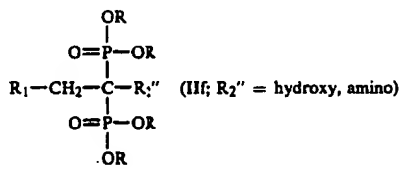
$$R_1—CH_2—COOH \quad (IIa)$$

or preferably the nitrile or acid chloride thereof, with a suitable triphosphite of formula $P(OR)_3$ (IIb), wherein R is e.g. lower alkyl, in the presence of a tri-lower alkylamine, e.g. triethylamine, to give an intermediate, presumably a compound of formula



(IIc; R_2' = oxo, imino)

and subsequently reacting said compound with a diphosphite of formula $H—P(=O)(OR)_2$ (IId) or $P(OH)(OR)_2$ (IIe), wherein R is e.g. lower alkyl, in the presence of a di-lower alkylamine, e.g. diethylamine, or of an alkali metal lower alkanolate, e.g. sodium methanolate, to the corresponding compound of formula



(IIf; R_2'' = hydroxy, amino)

Compounds of formula IIa are obtained for example by converting a suitable compound of formula

$$R_1—CH_3 \quad (IIIa)$$

with a strong base, for example one of the metal bases mentioned in process variant (a), into the carbeniate salt, and reacting said salt with carbon dioxide, or by converting a compound of formula

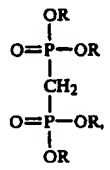
$$R_1—CH_2—Y \quad (IIg)$$

wherein Y is reactive esterified hydroxy, preferably halogen such as bromine, with an alkali metal cyanide, e.g. with sodium or potassium cyanide, into the corresponding nitrile (IIg; Y=CN), and hydrolysing the nitrile to the acid, preferably under basic conditions.

Starting materials II, wherein R_2 is hydrogen, are obtained for example by reacting a compound of formula

$$R_1—CH_2—Y \quad (IIg)$$

wherein Y is reactive esterified hydroxy, preferably halogen such as bromine, in the presence of a metal base such as the hydride, an amide or a hydrocarbon compound of an alkali metal, e.g. sodium hydride, sodium amide, ditrimethylsilyl sodium amide or butyl lithium, with a methane diphosphonate, e.g. of formula



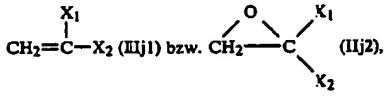
(IIh)

wherein R is for example lower alkyl.

Starting materials of formula II, wherein the radical R_1 is bound through a N-atom and R_2 is hydrogen or hydroxy, can also be prepared by reacting an appropriate compound of formula

$$R_1—H \quad (IIi),$$

in the presence of a strong metal base such as an alkali metal hydride or an alkaline earth metal hydride, e.g. sodium hydride, with a compound of formula



wherein X_1 and X_2 are preferably groups of formula IV.

Compounds of formula II, wherein R_2 is lower alkylthio or halogen, can be prepared for example starting from the corresponding compounds II, wherein R_2 is hydrogen, by converting these with a strong base, e.g. one of those mentioned above, into the carbeniate salt and subsequently reacting said salt with a lower alkylthio donor, for example a di-lower alkyl disulfide or a lower alkanesulfenyl chloride, or with a halogen donor, for example a halogen such as chlorine or bromine, perchloryl fluoride ($FClO_3$) or the like.

In starting materials of formula III for process variant (b), imino ether and imino ester groups are for example

those of formula —C(=NH)-X_3' (III'), wherein X_3' is etherified or esterified hydroxy such as lower alkoxy, a phenoxy group, lower alkanoyloxy, a benzoyloxy group or a halogen atom, e.g. a chlorine atom. Compounds of formula III, wherein X_3 is a group of formula III', can also be in the form of salts such as mineral acid salts, e.g. hydrohalides.

The reaction of compounds of formula III with phosphorous acid and phosphorus trichloride is carried out in conventional manner, such that the phosphorous acid component is preferably formed in situ by reacting excess phosphorus trichloride with aqueous phosphoric acid, e.g. with commercial phosphoric acid having a strength of about 75 to 95%, preferably of about 85%. The reaction is conveniently carried out with heating, e.g. in the temperature range from about 70° to 120° C., in a suitable solvent such as tetrachloroethane, trichloroethane, chlorobenzene, chlorotoluene or paraffin oil, and with working up by hydrolysis.

The starting materials of formula III, if not known, can be prepared for example by converting an appropriate compound of formula

$$R_1—CH_3 \qquad (IIIa)$$

with a strong base, for example with one of the metal bases mentioned in process variant (a), into the carbeniate salt and reacting said salt with carbon dioxide or with a compound of formula Y-X_3 (IIIb), wherein Y is halogen such as chlorine or bromine, e.g. with a carbamyl halide, imino ether halide or, preferably, with a cyanogen halide such as cyanogen chloride.

For the temporary protection of a N-atom of the radical R_1 which is capable of substitution there may be suitably employed the customary N-protective groups and methods of introducing and removing same, for example di-lower alkoxymethyl groups such as dimethoxymethyl, which can be removed by treatment with an acid, and 2,2,2-trihaloethoxycarbonyl radicals such as 2,2,2-triiodo-, 2,2,2-tribromo- or 2,2,2-trichloroethoxycarbonyl radicals, which may be removed for example by treatment with zinc in acetic acid, α-phenyl-lower alkoxycarbonyl radicals such as carbobenzoxy or trityl, which can be removed for example by catalytic hydrogenation, as well as lower alkanesulfonyl groups such as methanesulfonyl, which can be removed for example by treatment with bis(2-methoxyethoxy) sodium aluminium hydride; and also α-phenylalkyl or alkyl groups, the removal of which will be discussed below.

Compounds of formula I obtained by the process of this invention or by other per se known processes can be converted into other compounds of formula I in a manner known per se.

Thus, for example, compounds of formula I, wherein R_2 is amino, can be converted by treatment with nitrous acid into the corresponding compounds of formula I', wherein R_2 is hydroxy. The treatment with nitrous acid is effected in conventional manner with formation of same in aqueous solution from a salt thereof, e.g. from sodium nitrite, by treatment with an acid, e.g. hydrochloric acid, to form a corresponding unstable diazonium salt as intermediate, e.g. diazonium chloride, which splits off nitrogen upon introduction of the α-hydroxy group.

In compounds of formula I, wherein the radical R_1 is N-substituted by lower alkyl or by phenyl-lower alkyl which is unsubstituted or substituted by lower alkyl, lower alkoxy and/or halogen, it is also possible to remove the N-sustituent: lower alkyl for example by treatment with a haloformate such as a lower alkyl bromoformate or lower alkylchloroformate, and subsequent hydrolysis of the resultant carbamate, and α-phenyl-lower alkyl radicals by hydrogenolysis, e.g. treatment with hydrogen in the presence of a hydrogenation catalyst, e.g. palladium on carbon and/or platinum oxide, or by reduction with a metal, e.g. treatment with an alkali metal in ammonia.

Free compounds of formula I, including the inner salts thereof of formula I, can be converted into basic salts by partial or complete neutralisation with one of the bases mentioned at the outset. In similar manner, it is also possible to convert acid addition salts into the corresponding free compounds or their inner salts.

Conversely, free compounds of formula I can be converted into acid addition salts of formula I" by treatment with one of the protic acids mentioned at the outset.

Salts can be converted in a manner known per se into the free compounds, for example by treatment with an acid reagent such as a mineral acid, or a base, e.g. an alkali metal hydroxide solution.

The compounds, including their salts, can also be obtained in the form of hydrates or may contain the solvent used for crystallisation in their crystal structure.

Because of the close relationship between the novel compounds in the free form and in the form of their salts, the references made throughout this specification to the free compounds and their salts also apply by analogy to the corresponding salts and free compounds.

The invention also relates to those embodiments of the process in which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining steps are carried out, or a starting material is used in the form of a salt or, preferably, is formed under the reaction conditions.

In the process of this invention it is preferred to use those starting materials that result in the compounds described at the outset as being especially preferred. Novel starting materials and processes for the preparation thereof likewise constitute further objects of the invention.

The pharmaceutical compositions which contain the compounds of formula I, or pharmaceutically acceptable non-toxic salts thereof, are those for enteral such as oral, or rectal and parenteral, administration to warm-blooded animals, the pharmacological active ingredient being present alone or together with a pharmaceutically suitable carrier.

The novel pharmaceutical compositions contain e.g. from about 10 to 80%, preferably from about 20 to 60%, of the active ingredient. Pharmaceutical compositions for enteral or parenteral administration are e.g. those in dosage unit forms such as dragées, tablets, capsules or suppositories, as well as ampoules. These pharmaceutical compositions are prepared in a manner known per se, for example by conventional mixing, granulating, confectioning, dissolving or lyophilising methods. For example, pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, optionally granulating a resulting mixture and processing the mixture or granulate, if desired or necessary after the addition of suitable excipients, to tablets or dragée cores.

Suitable carriers are in particular fillers such as sugar, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, e.g.

tricalcium phosphate or calcium biphosphate, and also binders such as starch pastes, e.g. maize, corn, rice or potato starch, gelatin, tragacanth, methyl cellulose and-/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the abovementioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof such as sodium alginate. Excipients are in particular glidants and lubricants, for example silica, talcum, stearic acid or salts thereof such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable coatings which can be resistant to gastric juices, using inter alia concentrated sugar solutions which may contain gum arabic, talcum, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, shellac solutions in suitable organic solvents or mixtures of solvents or, for the preparation of coatings which are resistant to gastric juices, solutions of suitable cellulose preparations such as acetyl cellulose phthalate or hydroxypropyl methyl cellulose phthalate. Dyes or pigments can be added to the tablets or dragée coatings, for example to identify or indicate different doses of active ingredient.

Further pharmaceutical compositions for oral administration are dry-filled capsules made of gelatin and also soft sealed capsules consisting of gelatin and a plasticiser such as glycerol or sorbitol. The dry-filled capsules can contain the active ingredient in the form of granules, for example in admixture with fillers such as lactose, binders such as starches, and/or glidants such as talcum or magnesium stearate, and optionally stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in a suitable liquid, such as a fatty oil, paraffin oil or a liquid polyethylene glycol, to which a stabiliser can also be added.

Suitable pharmaceutical compositions for rectal administration are e.g. suppositories, which consist of a combination of the active ingredient with a suppository base. Examples of suitable suppository bases are natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols and higher alkanols. It is also possible to use gelatin rectal capsules which contain a combination of the active ingredient with a base material. Suitable base materials are e.g. liquid triglycerides, polyethylene glycols and paraffin hydrocarbons.

Particularly suitable dosage forms for parenteral administration are aqueous solutions of an active ingredient in water-soluble form, for example a water-soluble salt, and also suspensions of the active ingredient, such as corresponding oily injection suspensions, for which there are used suitable lipophilic solvents or vehicles such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, or aqueous injection suspensions which contain substances which increase the viscosity, for example sodium carboxymethyl cellulose, sorbitol and/or dextran, and optionally also stabilisers.

The present invention also relates to the use of the compounds of formula I and salts thereof preferably for the treatment of inflammatory conditions, primarily to diseases associated with impairment of calcium metabolism, e.g. rheumatic diseases and, in particular, osteoporoses.

Doses below 0.001 mg/kg of body weight affect pathological sclerosis and the decomposition of hard tissue only insignificantly. Long-term toxic side-effects may occur at doses of over 100 mg/kg of body weight. The compounds of formula I and salts thereof can be administered orally, as well as subcutaneously, intramuscularly or intravenously in hypertonic solution. Preferred daily doses are, for oral administration, in the range from about 0.1 to 5 mg/kg, for subcutaneous and intramuscular administration in the range from about 0.1 to 1 mg/kg and, for intravenous administration, in the range from about 0.01. to 2 mg/kg.

The dosage of the compounds of formula I and salts thereof is, however, variable and depends on the respective conditions such as the nature and severity of the illness, the duration of treatment and on the respective compound. Single doses contain for example from 0.01 to 10 mg; dosage unit form for parenteral, e.g. intravenous, administration contain e.g. from 0.01 to 0.1 mg, preferably from 0.02 to 0.08 mg; and oral dosage unit forms contain e.g. from 0.2 to 2.5 mg, preferably from 0.3 to 1.5 mg per kg of body weight. The preferred single dose for oral administration is from 10 to 100 mg and, for intravenous administration, from 0.5 to 5 mg. It is, however, possible to administer up to four single doses daily. The higher doses for oral administration are necessary on account of the limited absorption. In prolonged treatment, the dosage can normally be reduced to a lower level after an initially higher dosage in order to maintain the desired effect.

The following Examples illustrate the invention without in any way limiting the scope thereof.

EXAMPLE 1

With stirring and under reflux, 8.6 g (0.053 mole) of imidazol-4-ylacetic acid hydrochloride, 7.1 ml of 85% phosphoric acid and 25 ml of chlorobenzene are heated to 100° C. Then 13.9 ml of phosphorus trichloride are added dropwise at 100° C., whereupon evolution of gas occurs. Over the course of 30 minutes a dense mass precipitates from the reaction mixture. The batch is heated for 3 hours to 100° C. and the supernatant chlorobenzene is removed by decantation. With stirring and under reflux, the residual viscous mass is heated to the boil for 3 hours with 40 ml of 9N hydrochloric acid. The batch is filtered hot with the addition of carbon and the filtrate is diluted with acetone, whereupon the crude 2-(imidazol-4-yl)-1-hydroxy-ethane-1,1-diphosphonic acid precipitates. This product is recrystallised from water. Melting point: 238°–240° C. (dec.).

EXAMPLE 2

Reaction of 1-methylimidazol-2-ylmethyl bromide, benzylimidazol-2-ylmethyl chloride, (imidazol-1-methyl)toluenesulfonate, imidazol-4-ylmethyl chloride and thiazolyl-2-ylmethyl bromide with tetraethyl methanediphosphonate and hydrolysis of the resultant primary ethanediphosphonates in accordance with Example 9 or 12 also gives 2-(1-methylimidazol-2-yl)ethane-1,1-diphosphonic acid, m.p. 295° C. (dec.); 2-(1-benzylimidazol-2-yl)ethane-1,1-diphosphonic acid monohydrate, m.p. 181°–183° C.; 2-(imidazol-1-yl)ethane-1,1-diphosphonic acid, m.p. 255° C. (dec.); 2-(imidazol-4-yl)ethane-1,1-diphosphonic acid, and 2-(thiazol-2-yl)ethane-1,1-diphosphonic acid, m.p. 259° C. (dec.), and salts thereof, e.g. disodium salts.

EXAMPLE 3

The procedure of Example 1 is repeated, starting from 1-methylimidazol-2-acetic acid hydrochloride, to give 2-(1-methylimidazol-2-yl)-1-hydroxyethane-1,1-diphosphonic acid monohydrate, m.p. 261° C. (dec.).

The starting material can be prepared as follows: 0.5 g (0.032 mole) of 1-methyl-2-cyanomethylimidazole hydrochloride, 15 ml of glacial acetic and 15 ml of 36% hydrochlorid acid are heated for 24 hours to the boil under reflux. The reaction mixture is then evaporated to dryness under reduced pressure and the residue is taken up in 30 ml of hot glacial acetic acid and undissolved ammonium chloride is removed by filtration. The filtrate is concentrated by evaporation and the residue is taken up in acetone, affording 1-methyl-2-carboxymethylimidazole hydrochloride, m.p. 163°–164° C.

EXAMPLE 4

The procedure of Example 1 is repeated, starting from 4(5)-methylimidazol-5(4)-acetic acid hydrochloride, to give 2-[4(5)-methylimidazol-5(4)-yl]-1-hydroxyethane-1,1-diphosphonic acid, m.p. 217°–218° C. (dec.). The starting 4(5)-methylimidazol-5(4)-acetic acid hydrochlroide can be obtained in a manner similar to that described in Example 3.

EXAMPLE 5

The procedure of Example 1 is repeated, starting from 1-benzylimidazol-2-acetic acid hydrochloride and 1-methylimidazol-2-acetic acid hydrochloride, to give respectively 2-(1-benzylimidazol-2-yl)-1-hydroxyethane-1,1-diphosphonic acid of m.p. 171° C. (dec.), and 2-(1-methylimidazol-2-yl)-1-hydroxyethane-1,1-diphosphonic acid monohydrate of m.p. 261° C. (dec.), and salts thereof, e.g. sodium salts. The starting 1-benzylimidazol-2-acetic acid hydrochloric acid, m.p. 124°–125° C., can be obtained in a manner similar to that described in Example 2.

EXAMPLE 6

14.8 g (0.051 mole) of tetraethyl methanediphosphonate are added dropwise to a suspension of 2.4 g of sodium hydride in 35 ml of absolute tetrahydrofuran, and the reaction mixture is stirred at room temperature until the evolution of gas has ceased. Then 11.3 g (0.0465 mole) of 1-benzyl-2-chloromethylimidazole hydrochloride are added in portions. With stirring, the reaction mixture is heated under reflux for 20 hours to the boil. Precipitated sodium chloride is then removed by filtration and the filtrate is concentrated by evaporation under reduced pressure to give crude tetraethyl (1-benzylimidazol-2-ylmethyl)-methanediphosphonate. 3.0 g (0.065 mole) of tetraethyl (1-benzylimidazol-2-ylmethyl)-methanediphosphonate and 12 ml of 36% hydrochloric acid are heated under reflux for 20 hours to the boil. The reaction mixture is then concentrated by evaporation and the residue is crystallised from aqueous methanol, to give 2-(1-benzylimidazol-2-yl)ethane-1,1-diphosphonic acid monohydrate of m.p. 181°–183° C. Yield: 80% of theory.

EXAMPLE 7

Following the procedure of Example 6, reaction of 1-methyl-2-chloromethylimidazole hydrochloride, 1-methyl-5-chloromethyl-1H-1,2,4-triazole hydrochloride, and 2-chloromethylthiazole hydrochloride to the corresponding tetraethyl ethanediphosphonates and subsequent ester cleavage with trimethylbromosilane in the described manner affords: 2-(1-methylimidazol-2-yl)ethane-1,1-diphosphonic acid, m.p. 295° C. (dec.), 2-(1-methyl-1H-1,2,4-triazol-5-yl)ethane-1,1-diphosphonic acid, m.p. 274°-275° C., 2-thiazol-2-yl)ethane-1,1-diphosphonic acid, m.p. 259° C. (dec.), and salts thereof, e.g. disodium salts, and hydrates.

The starting 1-methyl-5-chloromethyl-1H-1,2,4-triazole hydrochloride can be prepared as follows: 11.1 g (0.10 mole) of 5-hydroxymethyl-1-methyl-1H-1,2,4-triazole are dissolved in 25 ml of dichloromethane. While cooling with ice and with stirring, 29.7 g of thionyl chloride are added dropwise. The reaction mixture is then stirred for 1 hour at room temperature and thereafter for 20 minutes at boiling temperature under reflux. The precipitate is filtered with suction, washed with diethyl ether and vacuum dried. Melting point: 136°–137° C.

EXAMPLE 8

The procedure of Example 1 is repeated, starting from 1-imidazoleacetic acid hydrochloride, 1-(1H-1,2,4-triazole)acetic acid hydrochloride and 1-pyrazoleacetic acid hydrochloride, to give the following compounds: 2-(imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid, m.p. 239° C. (dec.), 2-(1H-1,2,4-triazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid, m.p. 255° C. (dec.) and 2-(pyrazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid, m.p. 234° C. (dec.).

EXAMPLE 9

3.3 g (0.0072 mole) of tetraethyl 2-(benzylimidazol-2-yl)ethane-1,1-diphosphonate are dissolved in 50 ml of liquid ammonia and, with stirring, 1.0 g of sodium is added gradually in small portions until the blue colour of the solution is maintained for some time. Then 2.35 g of ammonium chloride are added in portions. The ammonia is then removed by evaporation, the residue is taken up in diethyl ether, the solution is filtered and the filtrate is concentrated by evaporation, affording tetraethyl 2-(imidazol-2-yl)ethane-1,1-diphosphonate as a colourless oil.

2.3 g (0.0062 mole) of tetraethyl 2-(imidzol-2-yl)ethane-1,1-diphosphonate are dissolved in 20 ml of methylene chloride. To the solution are added 4.8 ml of trimethylbromosilane and the reaction mixture is allowed to stand for 24 hours at room temperature and then concentrated by evaporation under reduced pressure. The residue is crystallised from 10 ml of methanol and 1 ml of water, to give 2-(imidazol-2-yl)ethane-1,1-diphosphonic acid of m.p. 279°–282° C. (dec.).

EXAMPLE 10

With stirring and under reflux, 8.6 g (0.053 mole) of imidazol-1-ylacetic acid hydrochloride, 7.1 ml of 85% phosphoric acid and 25 ml of chlorobenzene are heated to 100° C. Then 13.9 ml of phosphorus trichloride are added dropwise at 100° C., whereupon evolution of gas occurs. Over the course of 30 minutes a dense mass precipitates from the reaction mixture. The batch is heated for 3 hours to 100° C. and the supernatant chlorobenzene is removed by decantation. The residual viscous mass is heated for 3 hours to the boil, with stirring and under reflux, with 40 ml of 9N hydrochloric acid. The batch is then filtered hot with the addition of carbon and the filtrate is diluted with acetone, whereupon the crude 2-(imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid precipitates. This product is recrystallised from water. Melting point: 239° C. (dec.). Yield: 41% of theory.

EXAMPLE 11

The procedure of Example 9 is repeated, starting from tetraethyl 2-(pyrazol-1-yl)ethane-1,1-diphosphonate and tetraethyl 2-(imidazol-1-yl)ethane-1,1-diphosphonate. Treatment with trimethylbromosilane and working up with aqueous methanol gives 2-(pyrazol-1-yl)ethane-1,1-diphosphonic acid, m.p. 227° C. (dec.), and 2-(imidazol-1-yl)ethane-1,1-diphosphonic acid, m.p. 255° C. (dec.).

The starting esters can be prepared e.g. as follows: 0.10 g of sodium hydride is suspended in 4.0 ml of absolute tetrahydrofuran. A solution of 0.27 g (0.04 mole) of pyrazole in 2.0 ml of tetrahydrofuran is slowly added dropwise and to the clear reaction solution are added 1.2 g of tetraethyl vinylidenediphosphonate and the reaction mixture is kept for 24 hours at room temperature. Then 2 ml of 2N ethanolic hydrochloric acid are added. Precipitated sodium chloride is removed by filtration and the filtrate is concentrated by evaporation.

EXAMPLE 12

The procedure of Example 10 is repeated, starting from 0.05 mole of 4H-1,2,4-triazol-2-ylacetic acid, to give 2-(4H-1,2,4-triazol-4-yl)-1-hydroxyethane-1,1-diphosphonic acid of m.p. 255° C. (dec.) and salts thereof, e.g. disodium salts.

EXAMPLE 13

Reaction of (imidazol-1-ylmethyl) p-toluenesulfonate with tetraethyl methanediphosphonate and hydrolysis of the primary ethanediphosphonate in accordance with Example 2 gives 2-(imidazol-1-yl)ethane-1,1-diphosphonic acid of m.p. 255° C. (dec.) and salts thereof, e.g. the disodium salt.

EXAMPLE 14

Following the procedure of Example 3, 1-benzyl-2-carboxymethylimidazole hydrochloride of m.p. 124°–125° C. is obtained from 1-benzyl-2-cyanomethylimidazole.

Following the procedure of Example 10, 2-(1-benzylimidazol-2-yl)-1-hydroxyethane-1,1-diphosphonic acid of m.p. 171° C. (dec.) is obtained from 1-benzyl-2-carboxymethylimidazole hydrochloride.

EXAMPLE 15

3.4 g (0.0094 mole) of 2-(1-benzylimidazol-2-yl)-1-hydroxyethanediphosphonic acid are dissolved in 40 ml of liquid ammonia and then 1 g of sodium is added gradually, with stirring, in small portions until the blue colour of the solution is maintained for some considerable time. Then 2.35 g of ammonium chloride are added in portions. The ammonia is then removed by evaporation, the residue is taken up in 20 ml of hot water, the solution is filtered and then 10 ml of concentrated hydrochloric acid are added to the filtrate. The precipitated crystals are isolated by filtration and recrystallised from aqueous methanol, to give 2-(imidazol-2-yl)-1-hydroxyethanediphosphonic acid of m.p. 235° C. (dec.).

EXAMPLE 16

3.59 g (0.01 mole) of 1-amino-2-(1-benzylimidazol-2-yl)ethane-1,1-diphosphonic acid are dissolved in 20 ml of 1N sodium hydroxide solution, 0.82 g of sodium nitrite is added, and the solution is cooled to 0° C. With stirring, 18 ml of 2N hydrochloric acid are slowly added dropwise. Stirring is continued for 1 hour at 0°–10° C. and the precipitated product is isolated by filtration. Recrystallisation from water gives 2-(1-benzylimidazol-2)-1-hydroxyethane-1,1-disphosphonic acid of m.p. 171° C. (dec.).

EXAMPLE 17

In accordance with the procedures described in Examples 1 to 16 it is also possible to prepare 2-[2-methylimidazol-4(5)-yl]-1-hydroxy-ethane-1,1-diphosphonic acid, m.p. 261°–262° C. (dec.); 2-[2-phenylimidazol-4(5)-yl]-1-hydroxy-ethane-1,1-diphosphonic acid, m.p. 223°–224° C.; 2-(4,5-dimethylimidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid, m.p. 251°–252° C., and 2-(2-methylimidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid, m.p. 245°–246° C. (dec.), and salts thereof, e.g. disodium salts.

EXAMPLE 18

With stirring and under reflux, 11.95 g of 2-phenylimidazol-4-ylacetic acid hydrochloride, 7.1 ml of 85% phosphoric acid and 25 ml of chlorobenzene are heated to 100° C. Then 13.9 ml of phosphorus trichloride are added dropwise at 100° C., whereupon evolution of gas occurs. Over the course of 30 minutes a dense mass precipitates from the reaction mixture. The batch is heated for 3 hours to 100° C. and the supernatant chlorobenzene is removed by decantation. With stirring and under reflux, the residual viscous mass is heated to the boil for 3 hours with 40 ml of 9N hydrochloric acid. The batch is filtered hot with the addition of carbon and the filtrate is diluted with acetone, whereupon the crude 2-(2-phenylimidazol-4-yl)-1-hydroxyethane-1,1-diphosphonic acid precipitates. This product is recrystallised from water, yielding the sesguihydrate of m.p. 223°–224° C.

EXAMPLE 19

10 ml of 2N aqueous sodium hydroxide solution are added, with stirring, to a suspension of 3,36 g of 2-(2-phenylimidazol-4-yl)-1-hydroxy-ethane-1,1-diphosphonic acid in 10 ml of water. The resulting solution is evaporated to dryness. The residue is triturated with 40 ml of methanol. The crystalline precipitate formed is filtered off and dried yielding disodium 2-(2-phenylimidazol-4-yl)-1-hydroxyethane-1,1-diphosphonate-dihydrate m.p. 281°–283° C. (dec.).

EXAMPLE 20

In an analogous manner as described in Example 19, the following disodium salts can be prepared: disodium 2-(2-methylimidazol-4-yl)-1-hydroxy-ethane-1,1-diphosphonate-monohydrate, m.p. 292°–295° C. (dec.); disodium 2-(2-methylimidazol-1-yl)-1-hydroxy-ethane-1,1-diphosphonate-dihydrate, m.p. 295°–297° C. (dec.); disodium 2-(4,5-dimethylimidazol-1-yl)-1-hydroxy-ethane-1,1-diphosphonate-dihydrate, m.p. 286°–290° C. (dec.); disodium 2-(imidazol-1-yl)-1-hydroxy-ethane-1,1-diphosphonate-dihydrate, m.p. 291°–293° C. (dec.) and disodium 2-(pyrazol-1-yl)-1-hydroxy-ethane-1,1-diphosphonate-monohydrate, m.p. >300° C. (dec.).

EXAMPLE 21

A solution of 0.121 g of tris(hydroxymethyl)methylamine in 2 ml of water is added to a solution of 0.141 g of 2-(imidazol-1-yl)-1-hydroxy-ethane-1,1-diphosphonic acid in 1 ml of water. The resulting solution is concentrated by evaporation in vacuo and triturated with 6 ml of warm methanol. After cooling, a cristalline precipi-

tate is formed which is filtered off and dried for 1 hour in vacuo at 80° yielding pure mono-tris(hydroxymethyl)methylammonium 2-(imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonate of m.p. 170°–175°.

EXAMPLE 22

In an analogous manner as described in Example 21 the following tris(hydroxymethyl)methylammonium salts can be prepared: di-tris(hydroxymethyl)methylammonium 2-(imidazol-4-yl)-1-hydroxy-ethane-1,1-diphosphonate, m.p. 116°–117° C. (dec.); di-tris(hydroxymethyl)methylammonium 2-(4,5-dimethylimidazol-1-yl)-1-hydroxy-ethane-1,1-diphosphonate-monohydrate m.p. 110°–113° C. (dec.); di-tris(hydroxymethyl)methylammonium 2-(5-methylimidazol-4-yl)-1-hydroxy-ethane-1,1-diphosphonate, m.p. 122°–126° C. (dec.) and di-tris(hydroxymethyl)methylammonium 2-(1-benzylimidazol-1-yl)-1-hydroxy-ethane-1,1-diphosphonate-monohydrate, m.p. >300° C. (dec.).

EXAMPLE 23

Tablets containing 100 mg of active ingredient, e.g. 2-(imidazol-4-yl)-1-hydroxyethane-1,1-diphosphonic acid or a salt thereof, e.g. the disodium salt, can be prepared as follows:

Composition (for 100 tablets)	
active ingredient	100.0 g
lactose	100.0 g
corn starch	47.0 g
magnesium stearate	3.0 g

Procedure

All the solid constituents are sieved through a sieve having a mesh size of 0.6 mm. The active ingredient is then mixed with lactose, talcum, magnesium stearate and half of the starch in a suitable mixer. The other half of the starch is suspended in 40 ml of water and the suspension is added to a boiling solution of polyethene glycol in 100 ml of water. The resultant mixture is granulated, if necessary with the further addition of water. The granulate is dried overnight at 35° C., sieved through a sieve having a mesh size of 1.2 mm, and compressed to tablets of 6 mm diameter which are concave on both sides.

In like manner, tablets each containing 100 mg of another compound of formula I obtained in Examples 1–22 can also be prepared which compounds may also be in the form of salts with bases, e.g. as sodium salt.

EXAMPLE 24

Lozenges containing 75 mg of active ingredient, e.g. 2-(imidazol-4-yl)-1-hydroxyethane-1,1-diphosphonic acid or a salt thereof, e.g. the disodium salt, can be prepared as follows:

Composition (for 100 tablets)	
active ingredient	75.0 g
mannitol	230.0 g
lactose	100.0 g
talcum	21.0 g
glycine	12.5 g
stearic acid	10.0 g
saccharine	1.5 g
5% gelatin solution	q.s.

Procedure

All solid ingredients are first sieved through a sieve having a mesh size of 0.25 mm. The mannitol and lactose are mixed, the mixture is granulated while adding gelatin solution, sieved through a sieve having a mesh size of 2 mm, dried at 50° C. and once more sieved through a sieve having a mesh size of 1.7 mm. The active ingredient, glycine and saccharine are carefully mixed, then the mannitol, lactose granulate, stearic acid and the talcum are added. All the ingredients are thoroughly mixed and compressed to lozenges having a diameter of about 10 mm which are concave on both sides and provided with a breaking notch on the topside.

In like manner, lozenges containing 75 mg of another compound of formula I obtained in Examples 1–22 can also be prepared, which compounds can also be in the form of salts with bases, e.g. the sodium salt.

EXAMPLE 25

Tablets containing 10 mg of active ingredient, e.g. 2-(imidazol-4-yl)-hydroxyethane-1,1-diphosphonic acid or a salt thereof, e.g. the disodium salt, can be prepared as follows:

Composition (for 1000 tablets)	
active ingredient	10.0 g
lactose	115.7 g
corn starch	17.5 g
polyethylene glycol 6000	5.0 g
talcum	5.0 g
magnesium stearate	4.0 g
demineralised water	q.s.

Procedure

The solid constituents are sieved through a sieve having a mesh size of 0.6 mm. The active ingredient is then mixed with lactose, talcum, magnesium stearate and half of the starch in a suitable mixer. The other half of the starch is suspended in 65 ml of water and the suspension is added to a boiling solution of polyethene glycol in 260 ml of water. The resultant paste is added to the powders and granulated, optionally with the further addition of water. The granulate is dried overnight at 35° C., sieved through a sieve having a mesh size of 1.2 mm, and compressed to tablets of 10 mm diameter with a breaking notch on the topside and which are concave on both sides.

In like manner, tablets containing 10 mg of another compound of formula I obtained in examples 1–22 can also be prepared, which compounds can also be in the form of salts with bases, e.g. the sodium salt.

EXAMPLE 26

Hard gelatin capsules containing 100 mg of active ingredient, e.g. 2-(imidazol-4-yl)-1-hydroxyethane-1,1-diphosphonic acid or a salt thereof, e.g. the disodium salt, can be prepared as follows:

Composition (for 1000 capsules)	
active ingredient	350.0 g
microcrystalline cellulose	30.0 g
sodium lauryl sulfate	2.0 g
magnesium stearate	8.0 g

The sodium lauryl sulfate is sieved through a sieve having a mesh size of 0.2 mm and added to the active ingredient (lyophilised) and both components are intimately mixed for 10 minutes. Then the microcrystalline cellulose is sieved through a sieve having a mesh size of 0.9 mm, added to the above mixture, and the ingredients are intimately mixed for 10 minutes. Finally, the magnesium is sieved through a sieve having a mesh size of 0.8 mm, added to the mixture, and all the ingredients are mixed for 3 minutes. Size 0 hard gelatin capsules (elongated) are filled with 390 mg of this mixture.

In like manner, capsules containing 100 mg of another compound of formula I obtained in Examples 1-22 can also be prepared, which compounds can also be in the form of salts with bases, e.g. the disodium salt.

EXAMPLE 27

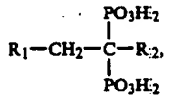
A 0.2% injection or infusion solution can be prepared e.g. as follows:

active ingredient, e.g. 2-(imidazol-4-yl)-1-hydroxyethane-1,1-di-phosphonic acid or a salt thereof	5.0 g
sodium chloride	22.5 g
phosphate buffer (pH = 7.4)	300.0 g
demineralised water to make up	2500.0 ml

The active ingredient is dissolved in 1000 ml of water and filtered through a microfilter. The buffer solution is added, followed by the addition of water to make up 2500 ml. To prepare dosage unit forms, 1.0 or 2.5 ml of the solution are filled into glass ampoules (each containing 2.0 or 5.0 mg of active ingredient).

What is claimed is:

1. A heteroarylalkanediphosphonic acid of the formula



(I)

wherein R_1 denotes an 1-imidazolyl or 2-(1-methyl-)imidazolyl radical and R_2 represents hydroxy, or a salt thereof.

2. A compound as claimed in claim 1 being 2-(imidazol-1-yl)-1-hydroxy-ethane-1,1-diphosphonic acid or a salt thereof.

3. A compound as claimed in claim 1 being 2-(1-methylimidazol-2-yll)-1-hydroxyethane-1,1-diphosphonic acid or a salt thereof.

4. A pharmaceutical composition for the treatment or prophylaxis of diseases associated with impaired calcium metabolism, containing a therapeutically effective amount of a compound claimed in claim 1 in the free form or in a pharmaceutically acceptable salt form, together with conventional pharmaceutical carriers.

5. A method of treating diseases associated with impaired calcium metabolism which comprises administering a therapeutically effective amount of a compound claimed in claim 1 in the free form or in a pharmaceutically acceptable salt form to a warm-blooded animal in need thereof.

* * * * *

APPENDIX E

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Maintenance Fee Statement

4939130

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMEI ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,939,130	184	2100	----	07/315,962	07/03/90	02/27/89	08	NO	PAID

ITEM NBR	ATTY DKT NUMBER
1	416180CIP

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APPENDIX E

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Maintenance Fee Statement

4939130

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

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If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,939,130	183	930	----	07/315,962	07/03/90	02/27/89	04	NO	PAID

ITEM NBR	ATTY DKT NUMBER
1	416180CIP

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APPENDIX F

Chronology of significant regulatory activities between Applicant and FDA during the IND and NDA periods:

IND PERIOD

08/12/93	Submitted original IND Application.
08/19/93	FDA LETTER (93-147) acknowledging receipt of the original IND which is assigned IND No. 43,240.
10/01/93	Submitted IRB approval and Informed Consent covering Protocol 01 for Dr. Siris.
11/03/93	Submitted IRB approval and Informed Consent covering Protocol 01 for Dr. Lyles.
11/17/93	Submitted unpublished preclinical report.
11/24/93	FDA LETTER (93-179) regarding the IND submitted August 12, 1993 and indicating that the study may proceed.
01/24/94	Submitted Amendment 01 to Protocol 1 which allows for enrollment of four completed patients at a higher dose levels of 400 µg of drug.
02/10/94	In response to concerns raised in FDA letter of November 24, 1993 submitted additional chemistry information and copy of the clinical label which complies with the FDA investigational label requirements. Also, in fulfillment of commitments made in the original IND, included the official English translation of documents regarding drug substance and drug product stability report.
03/02/94	Submitted new protocol: Protocol 02 and provided new investigator.

04/13/94	Amendment I to Protocol 02 and IRB approval for various investigators to cover Protocol 02 Amendment I.
04/19/94	Requested review of the protocol for a preclinical study.
05/19/94	Submitted additional chemistry and labeling information in response to FDA letter of November 24, 1993. Also included Stability Report.
06/03/94	Submitted for FDA review and assessment, a draft copy of the protocol for a preclinical study entitled "Effects of 16 months treatment with the bisphosphonate CGP 42446 on bone mineral density, bone mechanics and bone cell function in ovariectomized adult rhesus monkeys".
06/08/94	Provided for various investigators.
06/08/94	Submitted the following investigators for Protocol 02: Drs. Buckler, Davies, Fogelman, Fraser, Reid, Maricic, Moses, Singer and Siris, and Dr. Fazer.
06/10/94	Submitted final copy of the preclinical protocol entitled "Effect of 12 months treatment with the bisphosphonate CGP42446 on bone mineral density, bone mechanical properties and bone histomorphometric parameters in ovariectomized rats".
06/14/94	Submitted unpublished preclinical reports: "Disposition of 14C-labelled CGP 42446 in rats", Wiegand, H.
07/07/94	Submitted new investigators for participation in Protocol 02 and covering Protocol 02, Amendment I for Dr. Fraser.
07/18/94	Submitted Stability Report dated 6/30/94.
07/26/94	Submitted unpublished preclinical reports: C-G (Basle) Chemistry Support Report IL 7/1993, August 13, 1993, "CGP 42446: Synthesis of carbon-14 labelled compound", Laboratory Notebook Mo-57.3/Mo-57.4, Mory, H. and C-G (Basle) Toxicology Test 90-6190, 4/30/93, "CGP 42446B: 6-month oral toxicity study in dogs", Mertz, B. et al.

08/19/94	Provided documentation for Dr. R.D. Altman's (Miami, Florida Protocol 02) additional study site. Provided IRB approval for Amendment I for Dr. P. Selby's (Protocol 02) study site. Also submitted updated Form FDA 1572 to add new subinvestigators to Dr. M. Maricic's and Dr. A.M. Moses's Protocol 02 studies.
08/19/94	Submitted new investigators to Protocol 02.
08/26/94	Provided Amendment I to Protocol 03.
08/26/94	Submitted new protocol: Protocol 03 and provided new investigator.
10/05/94	Submitted unpublished preclinical report: Ciba TRE Report No. 94010, 9/8/94.
10/10/94	Annual Report covering the period of August 1, 1993 to August 1, 1994.
11/09/94	Submitted unpublished preclinical reports: C-G (Basle) Toxicology Test 92-6248, March 2, 1993, "CGP 42446: cytogenic test on Chinese hamster cells in vitro (EC-CONFORM)" and Toxicology Test 92-6297.
11/30/94	Submitted Final Medical Report for Protocol 001.
01/27/95	Submitted for FDA review a draft copy of a preclinical protocol.
01/30/95	Submitted Report No. 936059 advising of adverse teratological findings in rats.
02/15/95	Submitted new protocol, Protocol 003 extension. Also provided for Dr. Lipton who will conduct a study according to Protocol 003 extension. Provided for additional investigators who will conduct studies according to Protocols 02 and 03.
03/03/95	Submitted for FDA review a draft copy of preclinical protocol.

03/10/95	Submitted unpublished preclinical reports: C-G (UK) Preclinical Safety Report 024/93/SL, Test Number 936060, 9/23/94 and provided Final Report Amendment 1; submitted Preclinical Safety Reports 024/93/SL and 003/94/SL.
03/20/95	Provided documentation to support formulations; submitted stability information and an unpublished preclinical report.
03/23/95	Submitted request for review of the final version of the preclinical protocol and Amendments 1 & 2.
04/19/95	Submitted Amendment II to Protocol 03 and investigator documentation for Protocol 03.
04/19/95	Submitted Amendment I to Protocol 03 Extension and investigator documentation.
05/02/95	Submitted unpublished preclinical report: T/P Report 95004, (MIN 944073), Test No. 94-6024, 2/10/95.
05/09/95	FDA FAX (95-112) providing review comments of the Executive Committee for the Carcinogenicity Assessment Committee's recommendations for the doses in the rat carcinogenicity study. Also confirmed agreement on the doses used in the mouse carcinogenicity study (Amendments 024 & 025).
07/21/95	Provided background/reference material for August 14, 1995 meeting with FDA and submitted draft Protocol 017 which included preclinical and technical information.
08/16/95	Submitted IRB approval for Dr. James Berenson to cover Protocol 003, Amendment II.
08/25/95	Submitted CMC information and provided Stability Report dated 5/10/95.

08/31/95	As requested, provided a copy of the 8/14/95 meeting minutes and overheads used to discuss issues associated with the development of CGP 42446 in a transdermal formulation to treat patients with bone and postmenopausal osteoporosis.
10/27/95	Annual Report covering the period of August 1, 1994 to July 1, 1995.
12/04/95	Submitted unpublished preclinical report.
01/31/96	Requested FDA review and response to outlined concerns related to the clinical development of CGP 42446 for malignant indications.
02/05/96	Submitted new investigator to Protocol 03X: Dr. Berenson.
02/15/96	Submitted new Protocol 4244603007 in response to Mr. Hedin's (FDA) 2/13/96 request.
02/26/96	Submitted Amendment III to Protocol 003. Also IRB approval and patient consent form to cover the protocol amendment for Dr. Lipton, principal investigator.
03/22/96	Provided updated CMC information and Stability Reports.
03/28/96	Submitted Final Medical Report for Protocol 02.
05/22/96	Submitted unpublished preclinical report C-G Limited (Basle) Test No.: 93-6230, 1/12/96, "CGP 42446: 6/12-month subcutaneous toxicity study in rats," Meister, L., et al.
06/20/96	Advised the agency of improprieties discovered during a routine review of the study records at Dr. Berenson's site where he is conducting a study according to Protocol 003.
06/25/96	Amendment III to Protocol 03 which provides for the addition of two more dosing groups (4 mg and 8 mg dose).

07/09/96	Letter addressed to Dr. Williams advising him that as requested by the Division of Metabolism and Endocrine Drug Products, Ciba is providing him with a copy of all submissions relating to oncology indications of zoledronate and also a copy of Amendment 049 dated July 9, 1996.
07/09/96	Submitted new protocol – Protocol 4244603007 and provided new investigator: Dr. Morley.
07/17/96	Submitted toxicology reports and Toxicology/Pathology Test No. 926259, 2/3/95; Preclinical Safety Test No. 936063, 9/23/94; and unpublished preclinical reports: Ciba (Basle) Genetic Toxicology Report Test No. 926249, 7/7/93, CGP 42446: Gene Mutation Test with Chinese Hamster Cells V79 In Vitro, Galeick, D.
08/01/96	Submitted new investigators to Protocol 4244603007.
09/05/96	Submitted a new investigator to Protocol 03 Extension.
09/05/96	Submitted Amendment II to Protocol 03 Extension which allows for the monthly infusion of two additional dose groups (4000 µg and 8000 µg groups).
09/10/96	Submitted unpublished preclinical reports: C-G Limited, Basle, Preclinical Safety Report Test No. 936282, 10/24/94, CGP 42446: Local intravenous irritation study in rabbits, Nogues, V. and C-G Limited, Summit, NJ, U.S., Manuscript No. 96-0059, 4/15/96.
09/12/96	Submitted new investigators and a new subinvestigator to Dr. R. Dreicer's study.
10/21/96	Annual Report covering the period of July 1, 1995 to July 1, 1996.
11/14/96	Submitted an updated drug substance control document and a method validation.

11/22/96	Submitted IRB approval for Protocol 007, Amendment I and revised informed consent for Drs. Kuross, Dreicer, Morley and IRB approval for a revised informed consent for Dr. George.
11/22/96	Submitted documentation for investigators who will conduct a study according to Protocol 4244603007: Also included IRB approval for Amendment 1, revised informed consent and revised FDA 1572 to reflect the addition of two subinvestigators for Dr. Kardinal.
11/25/96	Sent letter addressed to Dr. Williams (FDA) indicating that as requested, Ciba is providing him a copy of amendment 057 to IND 43,240 dated November 22, 1996.
01/30/97	Provided investigators for Protocol 42446 03 007 and included IRB approval for revised consent for Drs. Kardinal and Morley; revised FDA 1572 to add two subinvestigators for Dr. Campbell and IRB approval for revised consent; also submitted IRB approval for Protocol 007, Amendment 1 and revised informed consent for Drs. Coleman and Young; Amendment 1 IRB approval for Drs. Keiser and Porter and an address change for the latter.
02/12/97	Submitted letter from Ciba transferring ownership of IND 43,240 to Novartis effective January 1, 1997 and letter from Novartis accepting ownership of the IND file from Ciba and identifying the new monitor of the IND.
02/24/97	Submitted preclinical report.
02/28/97	Submitted two investigators who will conduct a study in accordance with Protocol 007; noted that commercial Aredia (pamidronate disodium for injection) 90 mg sterile lyophilized vials manufactured by Ciba Pharmaceuticals, Summit, NJ will be used (H-3980); and included investigator signed Amendment 1 for Protocol 007 for Drs. Howell, Parker and Clarke..

03/24/97	Submitted documentation for drug substance manufactured by Synthesis D and the 4 mg powder for injection in vials, and provided a Stability Report.
03/28/97	Submitted new Protocol 035 and extension thereof and provided for Dr. Berenson who will conduct Protocol 035.
04/24/97	Submitted Protocol 007 Extension and a Form FDA 1572 for Dr. Morley.
04/25/97	TELEPHONE REPORT: Discussion with D. Spillman regarding the need for an additional IND for Zoledronate for the Oncology division.
05/05/97	Received FDA LETTER (97-105) regarding the 2/24/97 submission which provided the 26/52 week intravenous toxicity study. The study may continue but additional information is requested as outlined.
08/05/97	Submitted new investigators to Protocols 007, 007E and 07; subinvestigators to Protocol 03E study and new study site submitted.
08/06/97	TELEPHONE REPORT: Discussion with R. Hedin (M/E Division) regarding Zoledronate INDs and new IND in the Oncology Division.
09/19/97	Submitted response to FDA letter dated May 5, 1997 which requested response to comments regarding the 26/52 week intravenous toxicity study submitted on February 24, 1997.
09/24/97	Submitted investigators for Protocol 007 extension and new subinvestigators for Drs. Gibbons and Webb.
09/26/97	Submitted record of agreements reached during the September 17, 1997 telephone conference between FDA and Novartis to discuss the development plans for CGP 42446 for TIH.
10/01/97	Resubmitted serial no. 066, dated 8/5/97, in its entirety to the Division of Metabolic and Endocrine Drug Products. The contents of the submission was inadvertently sent to the Division of Oncology Drug Products.

10/02/97	Submitted new investigators to Protocol 007E: Drs. Fine and Rosen.
11/18/97	Submitted Annual Report covering period of July 1, 1996 through July 1, 1997 and Stability Report.
12/15/97	Submitted new investigators to Protocol 07E and 035E as well as new subinvestigators to Drs. Theriauet and Berenson's Protocol 007 study.
12/16/97	TELECON FROM FDA requesting that the BPK(CH) 1996/067 report be submitted for review.
12/18/97	Submitted new protocol: Protocol 4244604037 and submitted new investigators.
01/14/98	Submitted unpublished preclinical report: BPK (CH) 1996/067, 5/6/97, Plasma Concentrations of CGP 42446 During a 3-Month Intravenous Toxicity Study in Dogs.
01/20/98	Submitted new investigator to Protocol 007E and new investigators to Protocol 037.
01/26/98	TELECON FROM FDA: Approval of the compassionate use of zoledronate as requested by Novartis on January 26, 1998.
01/29/98	Formal request for compassionate use of zoledronate in the treatment of a single patient.
02/26/98	Added new investigators to Protocol 037.
04/01/98	Informed the agency that an updated investigator alert letter was issued.
04/02/98	Submitted new investigators for Protocol 037.
04/07/98	Request for compassionate use of zoledronate for the treatment of a single patient.
04/30/98	Provided for new investigators for Protocol 4244604037.

05/11/98	Response to FDA facsimile dated August 21, 1997 and response to FDA 12/8/97 telephone request for information concerning GI irritation.
06/11/98	Amendment 1 to Protocol 037.
06/17/98	Submitted new investigators to Protocol 4244604037.
07/02/98	Submitted draft Protocol 4244601005 and draft Extension Protocol.
07/22/98	Provided documentation for Dr. Levin participating in Protocol 037.
07/29/98	Submitted documentation for drug substance manufactured by Modified Synthesis D and documentation to support the addition of a new manufacturing site.
08/06/98	Provided table which includes the anticipated extent of zoledronate exposure data that will be available for the planned Paget's disease NDA filing based on the successful completion of Protocol 005 in response to FDA request of July 30, 1998.
08/14/98	FDA fax providing comments regarding the draft zoledronate Protocol 005 submitted July 2, 1998.
08/20/98	TELECON FROM FDA chemistry reviewer inquiring what phase Novartis has reached with the development of zoledronate. FDA suggested requesting a pre-NDA meeting especially with regard to the stability protocol.
08/26/98	Submitted new investigators to Protocol 42446037.
11/19/98	Submitted new investigators to Protocol 037.
11/23/98	Submitted new investigator to Protocol 037.
01/21/99	Requested a pre-NDA meeting to present an overview of Novartis' planned NDA submission.
02/11/99	Submitted new investigator to Protocol 037: Dr. Durie.

03/15/99	Submitted copies of a briefing documentation that includes a list of attendees, background information, and specific proposals for consideration for the meeting scheduled with the FDA on 4/15/99.
03/19/99	Submitted new investigators to Protocol 037.
03/25/99	Submitted general correspondence notifying the agency of the suspension of approval for Protocol 011 by the Local Ethics Committee in Great Britain.
04/09/99	Requested a pre-NDA meeting to discuss the CMC section of the NDA which Novartis anticipates to submit at the end of 1999 for treatment of patients with TIH.
04/15/99	Received minutes of the pre-NDA meeting dated April 15, 1999.
04/27/99	Submitted Annual Report for period August 31, 1997 through August 30, 1998.
05/04/99	Submission in response to an FDA request for information dated April 21, 1999 on the occurrence of lung cancer in randomized, placebo-controlled, trials in Paget's Disease, osteoporosis treatment, and osteoporosis prevention.
05/26/99	Submitted draft protocol for the proposed 2-week intravenous toxicity study in Sprague-Dawley rats.
05/27/99	Submitted briefing documentation in preparation for a meeting scheduled for June 22, 1999 to discuss the CMC section of a new NDA for zoledronate for treatment of patients with TIH.
06/02/99	Submitted new investigators to Protocol 037.
06/07/99	Received FDA FAX which includes pharmacology review comments regarding the May 26, 1999 submission, two week intravenous toxicity study in Sprague-Dawley rats.

06/22/99	FDA minutes of a pre-NDA meeting held on June 22, 1999 to discuss Novartis' proposals regarding the content and format of the CMC section of the NDA.
06/24/99	Submitted draft protocol for drug metabolism and pharmacokinetics study in rats. Also included response to FDA comments included in the June 7, 1999 facsimile regarding the 2 week i.v. toxicity study in rats, 5/26/99.
06/24/99	Submitted general correspondence in reference to the 4/15/99 pre-NDA meeting.
07/7/99	Submitted new investigators for Study No. 037.
07/15/99	Request for pre-clearance of proposed tradename, Zometa®/Zabel, in preparation for commericalization of this product. Background information on this product is provided to support the review.
07/19/99	Sent E-mail to FDA asking to communicate issues via e-mail concerning the NDA submission. Feedback was requested on previous issues (CMC and Clinical) as well as new issues (Statistical and General).
07/21/99	Submitted a draft study report (Study No. 997049), in response to a June 7, 1999 request.
07/22/99	TELECON from FDA indicating that the proposals detailed in our June 24, 1999 submission are acceptable. The statistician requests SAS efficacy programs as transport files with the NDA.
08/04/99	Submitted new investigator to Study 037: Dr. Hutchins.
08/17/99	Sent E-MAIL to FDA requesting a proposal to submit CRFs as previously defined but to limit NDA submission to those for the pivotal TIH trials (036 and 037) and the supportive study (CJ/HC1).
08/18/99	Received E-MAIL from FDA agreeing to CRFs proposal submitted in E-mail dated August 17, 1999.

09/21/99	Submission containing five serious adverse event reports that were submitted to IND 55,831 but inadvertently omitted from this IND.
09/23/99	Submitted request for an orphan drug designation for zoledronate in the treatment of TIH.
10/19/99	Sent E-MAIL to FDA containing several questions concerning the upcoming NDA.
10/26/99	Annual Report covering the period July 1, 1998 through July 1, 1999.
10/29/99	Resubmitted the September 23, 1999 request for orphan drug designation.
11/18/99	Received FDA LETTER acknowledging the submission for orphan designation and assigned reference number 99-1308.
12/06/99	Sent FAX to FDA containing 2 safety reports.
12/09/99	Sent FAX to FDA containing follow-up (#6.8) information.
12/15/99	Submitted investigator report.
12/21/99	Submitted investigator follow-up #3.4.
12/22/99	Letter to FDA authorizing FDA to refer to this IND in support of IND to be filed by Dr. S.E. Bulun.
12/29/99	Submitted investigator follow-up #2.3.
01/03/00	Submitted investigator follow-up #1.2.
01/04/00	Sent correspondence informing the Office of Orphan Products Development that an NDA was submitted to the FDA on December 21, 1999.
01/07/00	Submitted Amendment No. 1 to the Investigator's Brochure dated December 23, 1999.

02/08/00	Submitted safety reports containing 9, 15-day reports previously submitted to this IND with respect to the issue of 'acute renal failure'. The contents of the investigator alert for this case is included and contains what actions Novartis has taken and will take.
02/15/00	Submitted a Proposed Pediatric Study Request for FDA's review and issuance of a Written Request for pediatric exclusivity for zoledronic acid for children with osteogenesis imperfecta (OA).

NDA PERIOD

12/21/99	An original NDA was submitted for Zometa® for the treatment of TIH. A request for priority review was made as well as a request for a 90-day post-submission conference regarding the general status of the review.
12/27/99	FDA LETTER acknowledging receipt of the original NDA.
01/07/00	Submitted amendment to the pending NDA containing the statistical analysis output tables and figures for the Clinical Study Report 037 (Appendix 5, Section 5.1.2).
01/20/00	FAX to FDA containing references to support pamidronate as the current treatment of choice for TIH and a copy of the Aredia package insert providing comparative data of pamidronate versus etidronate.
01/31/00	TELECON with FDA regarding verification of the testing sites listed in the summary table.
02/02/00	Submitted amendment containing clarifications to the manufacturing, packaging and control sites for the drug product.
02/02/00	E-Mail to FDA confirming that the therapeutic classification is IP (priority review) and that the Division does not anticipate an advisory committee hearing on this application.
02/04/00	FDA LETTER requesting information on the Clinical Pharmacology and Biopharmaceutics section of the original NDA.
02/11/00	In response to the FDA letter dated February 4, 2000, submitted 2 reports, which were originally included in Section 5 of the NDA, Section 6: DMPK (US) R98-106 and DMPK (CH) 1997/530.
02/16/00	FAX from FDA containing a preliminary draft of information requested from the Statistical Reviewer concerning the NDA.

02/18/00	Submitted to the Office of Medical Policy, DSI, the names and addresses of the investigators in Protocol 37 and 36, listed by center number.
02/22/00	FAX from FDA of the second draft of an information request from the Statistical Reviewer concerning the NDA.
02/25/00	FDA LETTER agreeing that the waiver submitted in the NDA dated December 21, 1999, is justified for pediatric studies.
02/28/00	Submitted amendment containing a complete response for additional information pertaining to the statistical section of the NDA.
03/07/00	E-MAIL to FDA providing the NONMEN command and control file requested.
03/08/00	TELECON from FDA statistical reviewer requesting additional data analyses from the NDA.
03/16/00	E-mail to FDA on a proposal to limit the CRFs and narratives to be submitted in the 120-day Safety Update due April 21.
03/17/00	E-mail to FDA requesting a teleconference to discuss the submission of an NDA amendment to include a correction for the variables BUN and BUN/Creatinine Ratio that are reported in Protocol 036, ISE and the ISS.
03/21/00	Submitted amendment containing updated stability reports for both the drug substance and drug product in accordance with an agreement reached with the Agency at the June 22, 1999 pre-NDA CMC meeting.
04/04/00	E-mail to FDA regarding the preferred format for the submission of the revised Bun/Creatinine ratio variable and to inquire about the acceptability of the proposed tradename and proposed carton and vial labels in preparation for launch.

04/07/00	Submitted an amendment in reference to an e-mail to FDA dated March 17, 2000 to include a correction to the NDA for the summaries of BUN and BUN/Creatinine Ratio data reported in the pooled analysis (ISE, Appendix 1) and the ISS.
04/13/00	Submitted amendment provides additional statistical analysis and data presentation as requested on March 8 and March 31, 2000.
04/13/00	Submitted request for approval to import the subject bulk product Zometa®, 4 mg vials, in anticipation of FDA approval.
04/14/00	Submitted amendment providing for a revision to the font size for the strength on the Zometa® vial label.
04/14/00	Submitted electronic version of January 7, 2000 amendment which provides for Appendix 5, Section 5.1.2 for Protocol 037 Clinical Study Report.
04/19/00	Submitted amendment providing for the 120-Day Safety Update.
04/20/00	Submitted amendment containing the final stability update report for the drug substance, Synthesis E.
04/27/00	Submitted response to an April 12, 2000 request, for electronic data sets for the tumor data in Reports 951021 and 951159.
04/28/00	Submitted amendment in response to FDA's request dated March 31, 2000, for additional statistical analyses and data presentations.
04/28/00	E-mail from FDA containing questions generated from the NDA review of Studies 036 and 037 including some other clinical reports.
05/02/00	FAX from FDA containing a pharm/tox request to the Precautions section of the package insert.
05/05/00	Submitted letter is in response to an FDA facsimile dated May 2, 2000 requesting additional information and revisions to the Precautions section of the proposed package insert.

05/05/00	FAX from FDA containing comments on the review of the microbiology section of the NDA.
05/08/00	FAX from FDA requesting individual historical tumor incidence control data from the rat and mouse.
05/10/00	Submitted CMC amendment requested by FDA on May 3, 2000.
05/11/00	Submitted a complete response to a May 8, 2000, facsimile request from FDA for historical control incidence information.
05/12/00	Submitted complete response to an April 28, 2000, FDA e-mail containing questions and comments from the statistical reviewer.
05/12/00	Submitted electronic data sets for carcinogenicity studies in response to a request from the Biostatistics reviewer on May 4, 2000.
05/12/00	E-mail to FDA attaching revised SAS transport files containing data from the two carcinogenicity studies as requested on May 4, 2000.
05/15/00	E-mail to FDA containing MSWord documents for appendices 1-12 in response to the May 12 response review comments/questions.
05/16/00	TELECON from FDA Biopharmaceutics Reviewer requesting information on Studies J001 and 503.
05/17/00	Submitted complete response to all Microbiological/Sterile Validation comments received on May 5, 2000.
05/18/00	E-mail to FDA regarding preliminary feedback from the Data Monitoring Board (DMB) on potential concerns relating to renal safety in the ongoing Zometa® studies in patients with bone metastases.
05/18/00	E-mail to FDA of PDF versions of the carton and vial labels if needed for review.
05/18/00	Submitted response to review questions of May 16, 2000.

05/22/00	TELECON to FDA Medical Reviewer in response to his review comments.
05/23/00	TELECON with FDA Biopharmaceutics reviewer concerning the location of data from each study that supports a statement in the proposed package insert.
05/23/00	E-mail from/to FDA concerning the location of exclusivity for Zometa®.
05/26/00	Submitted specificity of the zoledronic acid radioimmunoassay, in response to a May 24, 2000 voice mail from FDA.
05/31/00	Submitted response to a May 31, 2000 e-mail requesting narratives for patients who died in Studies 036 and 037.
05/31/00	TELECON and E-mail to FDA on DSMB concerns regarding renal adverse events and narratives for patients who died in Studies 036 and 037.
05/31/00	E-mails from/to FDA regarding unequal distribution of patients in Studies 036 and 037.
06/01/00	Submitted request for a teleconference to discuss an anticipated amendment concerning potential concerns relating to renal safety in the ongoing Zometa® studies in patients with bone metastases.
06/01/00	E-mail to FDA regarding correspondence to pending NDA (renal function deterioration) and to request a telcon.
06/02/00	Submitted a complete response to all CMC questions received on May 25, 2000.
06/07/00	FAX and E-mail to FDA containing information in preparation for the June 7, 2000, teleconference regarding potential concerns relating to renal safety.

06/08/00	FDA's minutes of the June 8, 2000, teleconference to discuss the unblinded data package on renal safety and it's effect on the review of the NDA.
06/09/00	Submitted analyses of unblinded data in reference to the assessment made by the Data Safety Monitoring Board and the Renal Advisory Board from three ongoing bone metastases clinical trials.
06/21/00	TELECON with FDA Project Manager to discuss unblinded data, tradename review and OI protocols.
06/27/00	TELECON from FDA requesting further clarification on 1) the method 'Appearance of Solution' 224-01S.02 and 2) characterization of the DS - the single crystal x-ray (STRU_MS_975_1, section 1.7).
08/08/00	Submitted a copy of a letter submitted to IND 43,240 in reference to the June 9, 2000, submission (Serial No.150) and to the June 28, 2000, teleconference.
08/08/00	FAX from FDA containing changes to the labeling based on the completion of the pharmacology review of the NDA.
08/14/00	Submitted a proposed package insert revised to reflect the change in infusion time from 5 to 15 minutes and precautions and administration recommendations to emphasizing safety measures for the use of Zometa®.
08/14/00	FAX from FDA containing comments and requests following completion of a preliminary review of renal toxicity.
08/15/00	FDA LETTER listing deficiencies in the biopharmaceutics section of the NDA and containing labeling comments concerning the biopharmacetics review.
08/18/00	Submitted a copy of a letter submitted to IND 43,240 in reference to the August 8, 2000 submission (Serial No.162) and the August 17, 2000, teleconference.

08/22/00	Response to an August 15, 2000, FDA letter, regarding the biopharmaceutics section of the NDA.
08/25/00	Request for a refund of the user fee regarding designation of orphan drug status.
08/25/00	Submitted a copy of a letter submitted to IND 43,240 in reference to an August 14, 2000, facsimile from the FDA and to an August 17, 2000, teleconference.
08/29/00	FAX to FDA containing a copy of an e-mail response regarding Dr. Hon's site and the attachment from the February 2, 2000, submission.
09/01/00	E-mail to FDA containing vial and carton labels.
09/08/00	Submitted safety update summarizing the information communicated since the April 19, 2000.
09/14/00	Submitted response to the preliminary preclinical labeling comments received August 8, 2000, by facsimile.
09/20/00	E-mails to FDA containing information on the ongoing Zometa® clinical trials.
09/21/00	Submitted copies of the cover letters of the unblinded data from the ongoing studies submitted to IND 43,240 in support of the pending NDA.
09/21/00	FDA LETTER finding the original NDA, as amended, approvable.
09/29/00	Correspondence submitted in reference to the September 21, 2000, approvable letter, notifying FDA of Novartis' intent to file an amendment and also requests a meeting to discuss the format and content of the amendment.
10/10/00	Submitted follow-up to the meeting request of September 29, 2000.

10/12/00	FAX to FDA containing the Form 356H which was inadvertently left off the October 10, 2000, submission.
11/06/00	Submitted briefing book for the End of Review Meeting scheduled for December 14, 2000.
12/13/00	Submitted materials in preparation for a Novartis End of Review Meeting scheduled with the Division for December 14, 2000.
12/14/00	FDA minutes of an End of Review meeting held on Dec. 14, 2000.
12/14/00	Novartis minutes of a Drug Regulatory Affairs and FDA meeting held on December 14, 2000 to discuss the safe use of Zometa® in Hypercalcemia of Malignancy.
12/21/00	Submission complying with Division request of December 14, 2000 and addressing some lingering concerns expressed in the approvable letter and the December 14 meeting.
12/22/00	Fax to FDA in response to request for slides presented at the December 14, 2000 Zometa® End of Review FDA Meeting.
02/01/01	TELECON from FDA with comments on the renal safety data submitted in December 2000 to support the lift of the clinical hold.
02/19/01	Submitted amendment providing Novartis' Complete Response to the Approvable Letter issued September 21, 2000. Reference is also made to a December 21, 2000 Novartis letter and a January 8, 2001 telephone call when FDA accepted Novartis' proposal for this Complete Response.
03/26/01	Submission made in reference is to a February 19, 2001 letter with Novartis' Complete Response to the Approvable Letter and in response to requests made in an FDA telecon on March 22, 2001.
03/27/01	FDA LETTER acknowledging receipt of the resubmission to the Zometa® application, submitted on February 19, 2001.

03/29/01	Submitted, in response to an FDA request, a diskette containing the Kaplan-Meier figures for the pre amendment period for Study 10.
04/02/01	Official copy of telefax dated March 30, 2001 containing the running text of the proposed package insert which complies to the September 8, 2000, requests from the Division.
04/09/01	Submitted, in response to an FDA request, an official copy of telefaxes dated April 4 and 6, 2001, which contained patient narratives found in Novartis' Complete Response submission dated February 19, 2001.
04/11/01	Submitted the correct Tables 4 and 5 of the Complete Response submitted on February 19, 2001 to the Approvable Letter, issued to Novartis on September 21, 2000.
04/11/01	Fax to FDA with an attached section entitled, "Update of Renal Event Analyses".
04/30/01	Submitted approved labeling for the EU and Australia in reference to the February 19, 2001, Complete Response to the Approvable Letter.
05/03/01	Submission of an electronic and paper copy of a revised draft package insert which highlights changes made from the electronic version of the draft PI sent to the Division on April 25, 2001.
05/16/01	Notification to FDA stating Novartis accepts the terms issued in the NO OBJECTION FOR IMPORTATION LETTER dated August 31, 2000 with a correction that the material will be packaged by Novartis at the Suffern, N.Y. facility.
05/30/01	FAX from FDA containing information on financial disclosure by clinical investigators.
05/31/01	Fax to FDA, as a follow-up to a May 30, 2001 teleconference, regarding clinical investigator's financial disclosure information.
05/31/01	FAX to FDA containing financial disclosure information.

06/01/01	Submission of an official copy of the May 31, 2001, facsimile on financial disclosure.
06/08/01	Fax from FDA with comments regarding the Zometa® label.
06/12/01	Submission in response to FDA labeling comments of June 8, 2001.
06/22/01	FAX from FDA containing labeling comments from the clinical review.
07/10/01	Sent, in response to an FDA request, official copies of the draft labeling.
07/17/01	TELECON to FDA to discuss the timing and status of the NDA review and the timing and type of the bone mets application to the Oncology Division.
08/03/01	In response to an FDA request, this general correspondence submission contains samples of the Zometa® carton for purposes of color clarification.
08/09/01	FAX to FDA concerning the agreement reached between FDA and Novartis to use a two-hour administration of Aredia for the TIH program.
08/16/01	Sent letter notifying the Division that the Phase 4 Commitment to conduct a pharmacokinetics and pharmacodynamics study in patients with impaired renal function has been completed.
08/20/01	Submitted final revised labeling (carton and PI) that reflects all agreed changes made during telephone conversations held on August 15-17 and 20, 2001.
08/20/01	Received FDA LETTER via fax approving the new drug application for the use of Zometa® for the treatment of hypercalcemia of malignancy.